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ORIGINAL ARTICLES

FACTORS AFFECTING THE SURVIVAL OF TRANSPLANTED TISSUES*

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The possibility that tissues transplanted from one individual to another may under special circumstances survive and function has recently become generally appreciated (Ferrebee and Merrill[17]). The considerable potential usefulness of transplants has led to a scrutiny of the special circumstances determining survival with a view toward controlling these conditions in a clinically acceptable manner. A literature and a lore on the subject have grown up, some of it published and some not. Our purpose will be to review the general outlines of the problem and to give an account of one avenue of study with which we have had some experience.

This will not be a discussion of isografts from one identical twin to another or from one member of an inbred strain of animals to another member of the same strain. We will be talking about transplantation from one individual to another or from one strain of animals to another across what would normally be a rigid barrier of histoincompatibility. This then will be a discussion of homografts, useful transfers from one individual to another across what is usually taken to be a normal and insurmountable immunologic barrier.

Evidence for the fact that the problem is primarily one of destroying or circumventing a normal immunologic barrier is quite satisfactory. The story really begins with Medawar and Gibson in 1943. In Glasgow in Colebrook's ward for burned patients they

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settled a primary and vital point: that grafts from one individual to another are sloughed with increasing rapidity as the size and frequency of the grafting is increased (Medawar[22]). Under usual conditions first-time skin grafts do well for 2 to 3 weeks in man, second grafts from the same donor do well for only one or 2 weeks and so on. The accelerated reaction to a second graft from the same donor is a criterion of importance. It attests the existence of a basic underlying immune mechanism. The accelerated reaction is present as a usual response to a second homograft in man and in animals.

Two ways of avoiding these usual reactions of immunity have emerged. The first is the embryologic. At this moment it seems to have little practical utility. But it has had careful study by Medawar and Billingham and may be used to point up the biology of the problem as a whole. The second avenue is the radiologic. It follows the well-known fact that radiation may be used to weaken immune responses, including those to homografts. It has practical utility and it carries dividends; that is, helpful hints of what to do in radiation disasters and in treatments involving heavy radiation or radiomimetic drugs, as in patients with leukemia.

Let us look first at the embryologic approach to homografts. Figure 1 shows a white Leghorn growing patches of red feathers. Figure 2 shows a white mouse growing a patch of brown fur. These observations are from Billingham's "Quantitative Study of Actively acquired Tolerance" (Billingham, Brent and Medawar[5]). They depend upon a phenomenon basic in embryologic development and in some ways the opposite of immunity; namely, tolerance. Let us develop this notion of tolerance. An individual is tolerant to himself; he will take grafts from himself, autografts. He will not take grafts from others, homografts. Therefore, he must know himself and as a corollary he must distinguish himself from foreigners. Some marker denoting "self" must be on his molecules and not present or different on the molecules of others. Sir MacFarlane Burnet in his little book with Fenner on immunity was one of the first to emphasize this point. Probably the marker of chief importance, admitting the possibility of several, has something to do with chromosomes or genes. Histocompatibility can be shown to be a genetic phenomenon, closely relatable in the mouse to a histocompatibility locus present on a particular chromosome (Snell[33]). It is presumed that a similar situation pertains in other species.

Pursue for a moment this idea of the nuclear origin of the antigen important in determining histocompatibility. Medawar has isolated from nuclei a nucleoprotein effective in stimulating immunity to homografts, that is in accelerating their slough (Billingham, Brent and Medawar[6]). For example, a deoxyribonucleic acid protein complex may be prepared from the nuclei of cells taken from one strain of mice. Its injection into members of another strain will cause these latter animals to give a secondary or accelerated immune response to a skin graft from the first strain, the strain of origin of the nucleoprotein. Sloughing will occur in 6 days whereas normally a primary graft would go for 10 days. The time difference is significant to $\pm$ 0.2 of a day and indicates that the injection of nucleoprotein has produced the kind of immunity that a primary graft would have produced.

The $64 question is, how do mice of one inbred strain recognize their own nucleoprotein and reject all others? There is a time in embryologic development when this ability to recognize

Fig. 1.—(Taken from **Billingham, R. E., Brent, L.,** and **Medawar, P. B.:** Quantitative Studies on Tissue Transplantation Immunity. III. Actively Acquired Tolerance. Philosophical Transactions of the Royal Society, London, **239**, 357, 1957.)

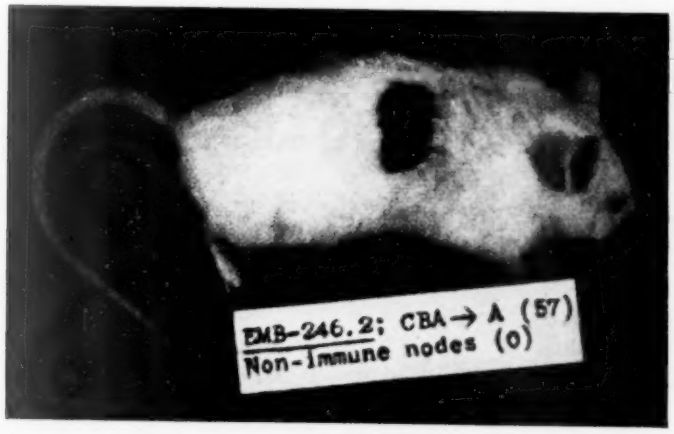

Fig. 2.—(Taken from **Billingham, R. E., Brent, L.,** and **Medawar, P. B.:** Quantitative Studies on Tissue Transplantation Immunity. III. Actively Acquired Tolerance. Philosophical Transactions of the Royal Society, London, **239**, 357, 1957.)

self is not yet present. Nature demonstrates this in cattle routinely (Owen[29]). Here in the bovine, vascular anastomoses exist between placentae of twins even when the twins originate from separate ova; that is, two eggs, two individuals genetically different, but with a placental communication. This communication permits exchange of cells in circulation, notably primitive blood cell precursors, at an early stage in embryologic development. In consequence, a condition of mutual tolerance of these cells emerges. The twins share the primitive cells, share blood groups and can be shown to exchange skin grafts or kidneys (Simonsen[30]) in later life, though being of diverse heredity and distinctly separate individuals. Tolerance acquired during fetal life extends beyond permanent growth of the tissue used to induce tolerance and embraces future acceptance of any other tissue of the same donor. The important antigen of homograft immunity is a nucleoprotein constituent peculiar to the nuclei of all cells of any given individual and presumably a direct reflection of his genetic chromosomal constitution (Medawar[23]). This fortunate universality of determinant antigen allows successful transplantation of other organs, such as skin and kidney, once tolerance to a single tissue, in this case bone marrow, has been established.

The same thing occurs occasionally in man (Dunsford *et al.*[13]) and can be produced artificially in many species by the technique of acquainting the developing embryo with a few cells of another strain; namely, by performing nature's own experiment through injecting these cells into the embryo's circulation at an appropriate period in development (Billingham, Brent and Medawar[5]). Actually in the rodent several hours of postnatal life or even days occur when tolerance may be actively acquired by this type of injection. A few million cells of the foreign strain intravenously is all that is needed. For example, the technique in the mouse shown, the one that took the skin graft from the normally histoincompatible brown strain (Fig. 2), was intravenous injection of a few buffy-coat nucleated cells (or it might have been spleen cells or skin cells since they all have the same nuclear antigen), a few hours after birth. Subsequent challenge by skin graft at a much later date, in adult life, showed acceptance of homograft as the slide indicated. Tolerance had been actively acquired by acquaintance with the essential nuclear antigen of the donor strain during a ductile stage of late embryologic development. In the chicken shown (Fig. 1), the technique was cross-circulation of a Leghorn and a Rhode Island Red egg while the embryos were developing (Hasek[18]).

The technique works for inducing tolerance to other antigens, proteins, bacterial products, *et cetera*, with varying time factors and quantitative relationships holding for different antigens and in different species (Billingham, Brent and Medawar[5]). The important thing is that it works for the essential antigen or antigens that reflect hereditary chromosomal constitution and determine in first order whether homografts are accepted.

A question arises whether the tolerance induced by the radiologic approach in adult animals is of similar origin. It is known of old that lymphoid organs: spleen and lymph nodes, Peyer's patches, and thymus are sensitive to radiation. It is also known that injection of cells from lymph nodes, from spleens and from peritoneal exudates will permit passive transfer of immunity of the homograft type just as they will transmit immunity of the tuberculin or delayed tissue sensitivity type (Mitchison[25]). Therefore, they

may be the cells whose destruction or alteration by radiation is necessary if tolerance is to be induced in the adult by radiation.

Let us consider an example of the importance of these lymphoid cells. Inject a mouse of strain A during adult life with cells of strain B or put a skin graft from B to A (all this, of course, in adult life without any prior embryologic or radiologic efforts at the induction of tolerance). The strain A member becomes immune to cells from strain B and sloughs his graft. Take spleen or lymph node cells from these immune members of strain A and inject these cells intravenously into some other members of strain A that have never met an antigen of the strain B type and are not immune to strain B. Since injection of lymphoid tissue from one A mouse to another A type mouse is an isologous transfer of cells among members of the same strain, no reaction

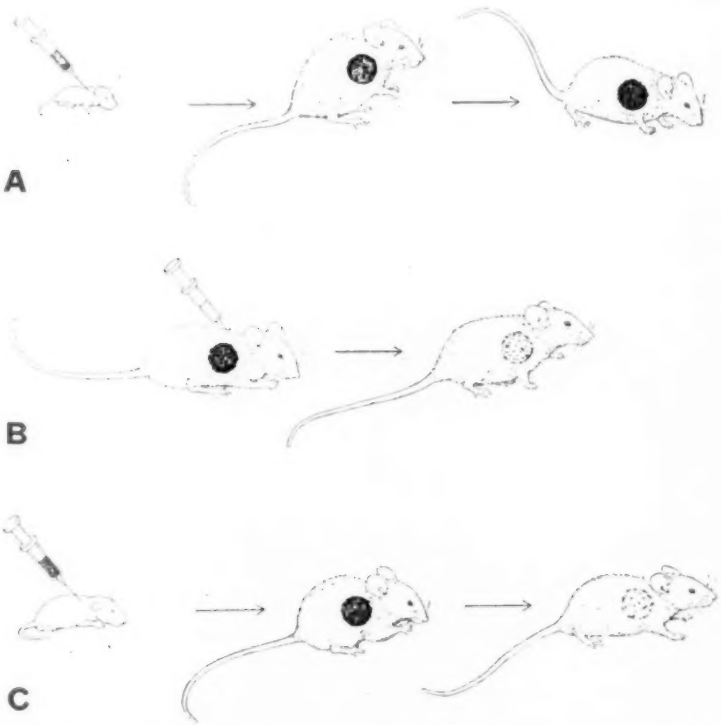

Fig. 3.—A. NEWBORN WHITE MOUSE is injected with spleen cells obtained from a brown mouse. If it is grafted later with skin from a brown mouse, the graft will "take" and remain intact for weeks or months just as if it had been taken from another part of the same mouse.

B. TOLERANT MOUSE, that is, a mouse which has accepted a graft after having been injected with spleen cells very shortly after birth, is injected with spleen cells from a normal mouse of its own strain. The mouse now rejects the graft it had accepted earlier.

C. SEVEN-DAY-OLD MOUSE does not become tolerant when injected with spleen cells from a brown mouse. On the contrary, it rejects grafts from the brown mouse more rapidly than usual. Adult white mice react in the same way to the injection. (Taken from **Medawar,** P. B.: Skin Transplants. Scientific American, April, 1957.)

of immunity occurs at this level of inbreeding. The donor lymph nodes or spleen cells from the immune members of strain A "home" in their new hosts. They go to and settle down in the lymph nodes and spleen,- the normal habitats or homes for these cells. But these homing cells came from members of strain A who were immune to strain B, and now the question arises, do these cells passively confer on their strain A hosts an immunity to strain B? The answer is they do. Grafts of strain B skin to these particular A animals now slough briskly in 6 days or less instead of lasting for 10; that is, the strain A mice have been passively immunized and they now give the accelerated immune response typical of a previously immunized and reactive animal.

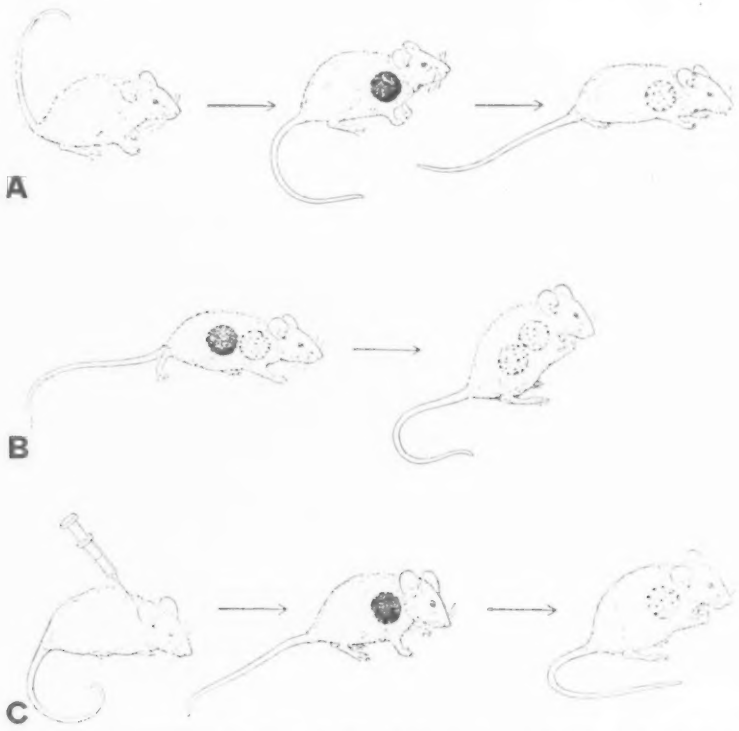

Fig. 4.—A. NORMAL WHITE MOUSE (*left*) which receives a skin graft from a brown mouse will reject it. The foreign skin disintegrates in about 10 days' time and falls off (*right*). Grafted skin from any other animal not an extremely close relative will also be rejected.

B. MOUSE WHICH HAS HAD A GRAFT will also reject a second one from the same donor. The second transplant and subsequent ones will disintegrate even more rapidly than the first. This occurs even when many months have passed between grafts.

C. INJECTION OF LYMPH CELLS obtained from mouse which had earlier rejected a graft is administered to a normal mouse. If this mouse later received a graft from a brown mouse, it will reject the graft as rapidly as the mouse which had had two grafts. (Taken from **Medawar, P. B.:** Skin Transplants. Scientific American, April, 1957.)

Two figures from an article by Medawar[24] summarize what we have been discussing (Figs. 3 and 4).

Since passive transfer of homograft immunity is achieved only with cells of lymphopoietic or reticular origin, interest in the fate of such cells on exposure to radiation heightens and it becomes significant that radiation of intensity sufficient to destroy lymphopoietic centers induces a state of ductility in which tolerance may be actively acquired in the adult just as in the fetus, though the mechanism may be different (Main and Prehn[21]). For example, consider this mouse (Fig. 5). He is of strain A. He has a skin graft from strain B that he is obviously tolerating and enjoying. How did he get that way? As an adult he was given lethal total body radiation, roughly 700 roentgens in a period of a half hour. This radiation stopped mitosis in erythropoietic tissue, in myelopoietic tissue, and in, let us say, *mature* elements of the lymphopoietic tissues. If let alone, the animal would die in 7 to 14 days of deficiency of formed elements of blood: bone marrow failure plus elements of immune mechanism failure, failure of lymphopoiesis, antibody formation, *et cetera*, as shown by overwhelming and fatal septicemia. But since the dose of radiation given was sufficient to knock out adequately his mechanisms for repelling invaders, he took a graft of foreign bone marrow cells of a different white strain mouse intravenously with success. These members of the foreign erythropoietic, myelopoietic, and to a certain extent lymphopoietic systems "homed" to their appropriate sites: bone marrow, spleen, lymph nodes, multiplied and formed active bone marrow and active lymphopoietic organs in time to save his life. But as a result he became an altered animal, a chimera, and would take grafts of any tissue from the white strain including skin as shown in the figure.

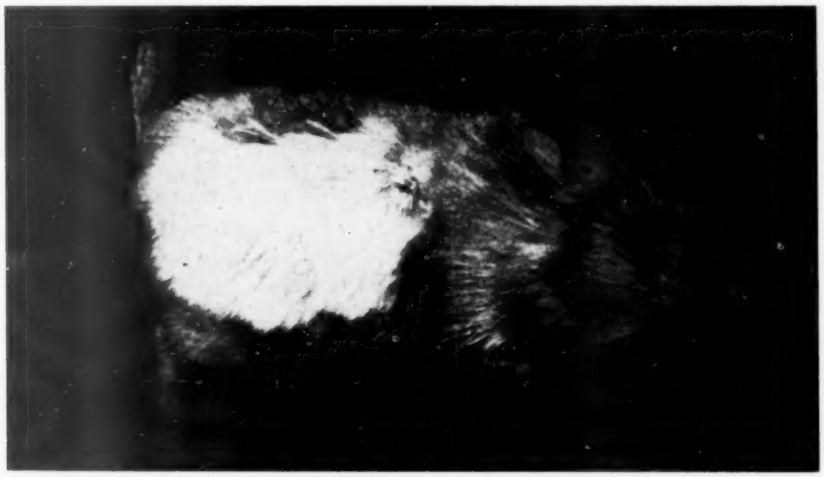

Fig. 5.—(Taken from **Main, J. M., and Prehn, R. T.:** Successful Skin Homografts After the Administration of High Dosage X-Radiation and Homologous Bone Marrow. J. Nat. Cancer Cancer Inst., **15**, 1023, 1955.)

Perhaps at this stage we ought to take up some of the quantitative problems of dose of radiation and dose of marrow: the number of roentgens needed to prepare the animal and the number of marrow cells needed to save his life. A large body of evidence shows

a necessity for using enough radiation to weaken the host's immune response and enough marrow as seeds to get the graft going quickly (Congdon, Makinodan and Gengozian[10]). The simile is agrarian. The more divergent, genetically speaking, the host and donor strains, the more deeply must be the field of lymphoid tissue be ploughed by heavy radiation and the more heavily must it be seeded by a large number of marrow cells. The radiation requirement in the rat-to-mouse system is distinctly greater than in the mouse-to-mouse system. And in the guinea pig-to-mouse and rabbit-to-mouse system it is even greater and begins to encroach upon the limits of radiation tolerance of the large and small intestines, a type of damage not to be repaired by marrow transplant and hence beyond the range of usefulness (Congdon[8]).

Things must be done just right. A crop of donor marrow must be forthcoming in time to save the host from acute radiation death and the intensity of radiation must not have produced other lethal effects such as breakdown of the intestinal barrier. Moreover, it can be shown that at several levels of inadequate radiation, injection of foreign marrow rather than being lifesaving becomes lethal (Trentin[37]). The partially knocked out host in these cases seems to spend his last energies fighting the graft in such manner that neither it nor his own residual marrow survives and he dies of marrow failure. Had he been given more radiation, he would have taken the foreign marrow, allowed it to survive and made the best of it. And when he did make a successful acceptance of the marrow graft, returning to our last mouse, Fig. 5 with the skin graft, he became tolerant to other tissues of the donor strain, since all these tissues have in all their cells the same nuclear antigen and are therefore not foreigners as far as his new system of recognition and defense is concerned.

In a sense, the irradiated and marrow-transplanted mouse has been taken over by a new army with a new password. His lymph nodes and spleen now yield to the marker or password of the donor strain and he will take adrenal or kidney or skin or what you will from that strain, but from that strain and his own alone. He has become a true chimera. Cells of different genotype, different hereditary chromosomal origin, are now living peaceably together or at any rate surviving together.

One says "surviving together" because the army of occupation does not seem always to be accepted as completely as one might wish. There is an erratic incidence of a wasting disease that from the appearance of burnt out lymph nodes and spleens with hemorhages seems to represent a smoldering immunologic struggle, the graft fighting the host and sometimes the host fighting the graft (Congdon and Urso[11]). This warfare, when it occurs, plus some elements of late radiation-damage that cause intestinal malabsorption (Mole[26]), produces an animal that looks a bit troubled and may die prematurely. However, chimeras of life span two-thirds normal do occur and look pretty good (Congdon[9]). At all events, death from acute post-radiative marrow failure is avoided by these techniques and useful homografts of other tissues may be tolerated for useful periods of life.

With this backlog of embryologic and zoologic information it may be reasonable for clinicians to see what adaptation can be made to clinical medicine as of now, realizing that there is much species variability that requires specific evaluation in man and also that there is much that is crude in an

approach to transplantation that in itself involves total body radiation. The approach, clumsy as it may be, however, is fair in the case of some patients. Some patients, notably some leukemics, are not going to be around next year or 10 years from now when a subtle specific approach to homografts may be forthcoming. Moreover, radiation if properly managed is a good treatment for these patients. This fact is important and should not be misunderstood. It is vital in clinical investigation to make the study in the interest of the individual studied and not just in the interest of science in general. We can do this with radiation and patients who now have leukemia.

Let us consider the problem of working with radiation and leukemic patients, since they are our most necessitous subjects. Radiomimetic compounds, nitrogen mustards, and marrow toxic agents of one kind or another seem less manageable than general radiation in homograft work and we will, therefore, leave drugs of this type out of present discussion.

The leukemic cell is in general susceptible to Roentgen-ray. Some strains more so than others, and most appreciably less susceptible than are normal marrow and normal lymphoid tissues. Otherwise, if this were not so, there would be no problem and leukemia would be routinely treated and cured by radiation. The real question to settle is whether a lifesaving marrow transplant can be made in man after the amount of radiation that is necessary to knock out the leukemic cell (Thomas *et al.*[36]).

It is encouraging to learn that with lethal radiation followed by lifesaving marrow transplantation some mice with some strains of leukemia have enjoyed clinical cure of their disease (Barnes *et al.*[2,3]). A cautious approach to total body radiation with gradually increasing dosage followed by marrow transplantation, therefore, seems sensible and perhaps in the interest of some patients. The going, as indicated by our preliminary experience (Thomas *et al.*[36]), however, is going to be rough. The amount of radiation required in man, as in the mouse, is considerable. Patients in the late stages of leukemia are sick unto death even without the trauma of radiation. Marrow grafts are probably not going to take well or grow rapidly in critically ill patients. It, therefore, is important to get plenty of marrow for transfusions so that the starting of a new crop after radiation will be as rapid as possible.

Marrow may be obtained from fetuses, from ribs removed at surgery, from aspiration of the sternum and ilium, and from adult patients at necropsy. The amounts obtainable are of the order of 1 or 2 billion nucleated cells except in the case of adult necropsy where suitable cadavers, coronary cases, et cetera, may yield 20 to 50 billion viable cells (Thomas *et al.*[36]).

Postmortem examinations for marrow procurement are performed under sterile conditions as soon as possible after death. Figure 6 shows what happens to marrow cells if too much time elapses before they are harvested (Thomas *et al.*[36]). The criterion of viability used in this figure is the rate of DNA synthesis. DNA, or deoxyribonucleic acid, is the essential constituent of nuclear chromatin; chromosomes. An increase in its synthesis is an obligatory antecedent to cell division. It may be seen from the slide that acceptable rates of DNA synthesis are still present in cells removed 4 to 6 hours after death. The problem, therefore, of getting good postmortem marrow in adequate amount is not overwhelming. And guessing from experiences in animals and in man one should try to

get 25 billion cells for a good transplant, the more the better.

Marrow does not keep well under tissue culture conditions *in vitro*, and no one has been able to grow it; that is, make it multiply *in vitro*. Marrow, however obtained, must be used quickly or stored in some acceptable fashion. Freezing to —80° C. in 15% glycerol has been found acceptable (Ferrebee *et al.*[15]). This trick of freezing in the presence of glycerol has been found useful for preserving for months, the viability of cells of many types: sperm, neoplasms, normal tissues, and marrow (Smith[32]).

We have investigated to some extent the freezing conditions specifically applicable to marrow (Smith[32]). Figure 7 depicts an effort to titrate the number of marrow cells that must be infused after lethal radiation, 700 to 900R, in order to get a high percentage of recovery, a low mortality, in mice. It may be seen that something in excess of 100,000 is necessary. The end point is not a sharp titration, but certainly 1 million cells is plenty and not a great excess. The glycerol low-temperature method of preservation (Barnes and Loutit[4]) works satisfactorily with mouse marrow within the limits of the titration achieved with fresh marrow. Mouse marrow frozen in glycerol and carried down to —80° C. at appropriate rates of cooling gives cells that on

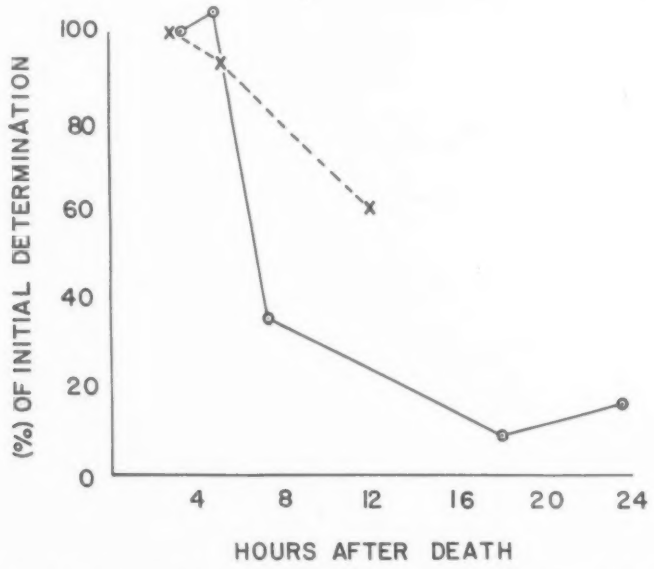

Fig. 6.—(Taken from **Thomas, E. D., Lochte, H. L., Jr., Lu, W. C.,** and **Ferrebee, J. W.**: Intravenous Infusion of Bone Marrow in Patients Receiving Radiation and Chemotherapy. New England J. Med., **257,** 491, 1957.)
Post-Mortem Change in the Rate of DNA Synthesis of Human Bone Marrow.
Bone marrow was removed from the ribs of 2 cadavers at intervals after death, suspended by the screen-syringe technique and incubated for 4 hours with C^{14}-labeled formate, and the specific activity of the initial sample 3 hours post mortem, plotted as 100%, corresponds closely to values obtained wih the use of fresh marrow from ribs removed at surgery. The incubation medium consisted of 50% normal human serum in Hanks's solution containing 1.0 microcurie and 0.5 micromol of C^{14}-labeled formate per milliliter.

thawing are as good as fresh cells in producing recovery in mice after lethal radiation (Ferrebee *et al.*[15]). The rates of cooling are important. Disproportions between volume changes and membrane surface area changes in certain temperature ranges produce lethal cracks and distortions if the rate of change is too rapid (Lovelock[20]).

with mouse marrow. By passing human marrow preparations repeatedly across fine stainless steel meshes one may break up clusters and prepare a satisfactory suspension of free cells (Thomas[35]). Infusion of this material has produced no trouble in 9 patients (Thomas *et al.*[36]). It is known that marrow cells hang up in the lung,

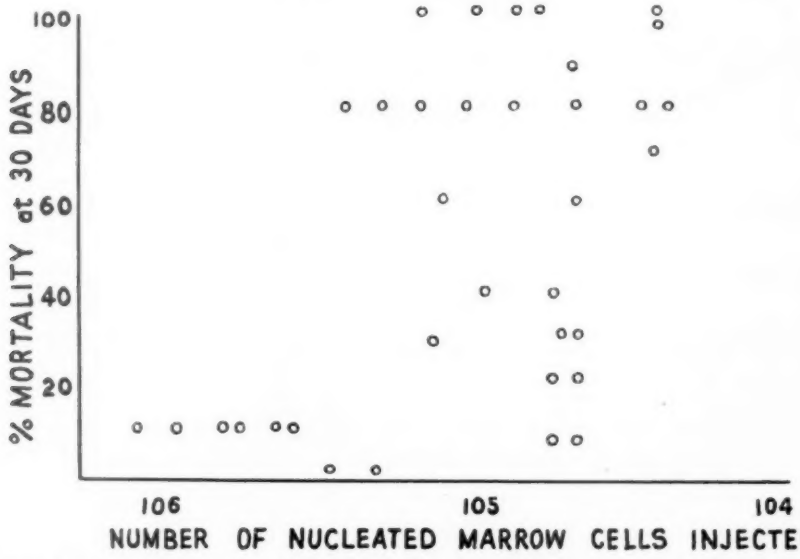

Fig. 7.—Mortality in C$_3$ H • 101)F$_1$ mice receiving lethal radiation (900 r) as affected by the number of fresh marrow cells from isologous donors. The marrow cells were injected intravenously shortly after radiation. Each point represents the results in a group of 10 animals. (Taken from **Ferrebee, J. W., Billen, D., Urso, I. M., Lu, W. C., Thomas, E. D.,** and **Congdon, C.:** Preservation of Radiation Recovery Factor in Frozen Marrow. By Permission from Blood, Dec. 1957, Vol. XII, No. 12, pp. 1096–1100.)

When working with cadaver marrow and human marrow in general, one must entertain a few other considerations. Human marrow needs to be freed from fat. This can be done by differential centrifugation. The fat comes to the top and can be creamed off. The normal marrow cell clumps or clusters also need to be broken up and a suspension of free cells prepared before the material is infused intravenously. These mechanical problems don't occur

liver, and spleen on their way to homing in the marrow spaces (Nowall *et al.*[28]). The degree of hang up in the lung is not troublesome with the screened marrow preparations. Evidence that marrow so prepared and frozen and thawed may be viable can be seen in Table 1 (Thomas *et al.*[36]). Here it is evident that the effect of screening, defatting, freezing, thawing, deglycerolizing[31] and resuspending in a solution of physiologic tonicity has not

completely ruined the ability of these human marrow cells to produce DNA; that is, their ability to prepare to divide. Also important to note is that freezing, thawing, and glycerol have affected the human cell less than the mouse cell. This is fortunate because by direct *in vivo* assay the mouse cell was demonstrated to be effective after freezing and thawing and deglycerolizing[15].

in this last patient are about what one would expect with a graft after the amount of radiation given, an amount useful in controlling his leukemia and adequate to permit temporary activity in the marrow graft during a critical period immediately following radiation.

We come, therefore, to the problem of giving greater amounts of radiation to man, enough possibly to produce cures of leukemia and permanent grafts.

TABLE 1.—A COMPARISON OF DNA SYNTHESIS BY HUMAN AND MOUSE BONE MARROW SUBJECTED TO VARIOUS FREEZING PROCEDURES*

		CPM/μM of Thymine isolated from DNA			
		Human		*Mouse*	
Freezing Technique	*Suspension Fluid Used*		*Average*		*Average*
Kept at 4° C.	Basic (with homologous serum)	19,000 18,200	18,600	3,340 3,950	3,645
Barnes *et al.* (2) frozen to −80° C., thawed at 37° C.	Basic (with homologous serum)	222 164	193	135 90	112
Kept at 4° C., then glycerol removed by Sloviter (7) procedure	Basic plus 15% glycerol	10,130 11,500	10,815	567 111	339
Barnes *et al.*, frozen to −80° C., thawed at 37° C., then glycerol removed by Sloviter procedure	Basic plus 15% glycerol	8,000 7,650	7,825	486 —	486
Kept at 4° C.	Basic plus 5% human albumin	23,600 —	23,600	3,780 3,920	3,850
Barnes *et al.*, frozen to −80° C., thawed at 37° C.	Basic plus 5% human albumin	184 —	184	180 82	131

*Taken from **Ferrebee, J. W., Billen, D., Urso, I. M., Lu, W. C., Thomas, E. D.,** and **Congdon, C. C.:** Preservation of Radiation Recovery Factor in Frozen Marrow. By Permission from Blood, Dec. 1957, Vol. XII, No. 12, Pp. 1096–1100.

Evidently the human cell is at least as tough as the mouse cell by *in vitro* test and ought, therefore, to do at least as well *in vivo*. Figure 8 shows that it does do well (Thomas *et al.*[36]). This C— patient received frozen C+ marrow after irradiation. C+ cells of donor type increased in number and constituted a major portion of the circulating red cell mass during the first few weeks after radiation. The results

Two factors of major importance in working with the radiation requirements of large animals (man and dogs) have been incorporated in the teletherapy unit shown in Fig. 9. The first is the use of two opposed and balanced beams of radiation and the second is the use of a high energy photon.

The availability of the above teletherapy unit with its two sources and high energy photons is believed to be

critical for studies in man. Many of the available data concerning bone marrow transplantation come from studies using small rodents, particularly mice. Two radiation sources are not necessary for the mouse because the small body mass absorbs only a very little of the radiation and hence the ratio of the intensity of the exit beam and incident beam is near unity. With man, appreciable absorption of radiation energy occurs and hence two symmetrically placed sources are necessary for homogeneous effects. That homogeneity is achieved is indicated by Fig. 10 showing isodose curves for two Co^{60} fields in opposition (Johns[19]).

A further problem in radiation studies on large animals is the inhomogeneity produced by density differences in soft tissue and bone. Figure 11 shows the homogeneity achieved inside bone cavities by using Co^{60} (1 MEV) radiation as compared to the usual 250 KV radiation (Spiers[34]). Accurate, well-defined, and uniform radiation to host cells concerned with immune mechanisms is essential for successful homotransplantation. The amount of radiation that these lymphoid cells receive, the amount of radiation that the leukemic cells require, and the amount of radiation beyond the marrow death dose that the patient can stand must be in careful adjustment. Since the cells with which we are concerned occur not only in soft tissue, but also in bone, high energy photons of the Co^{60} type are advantageous.

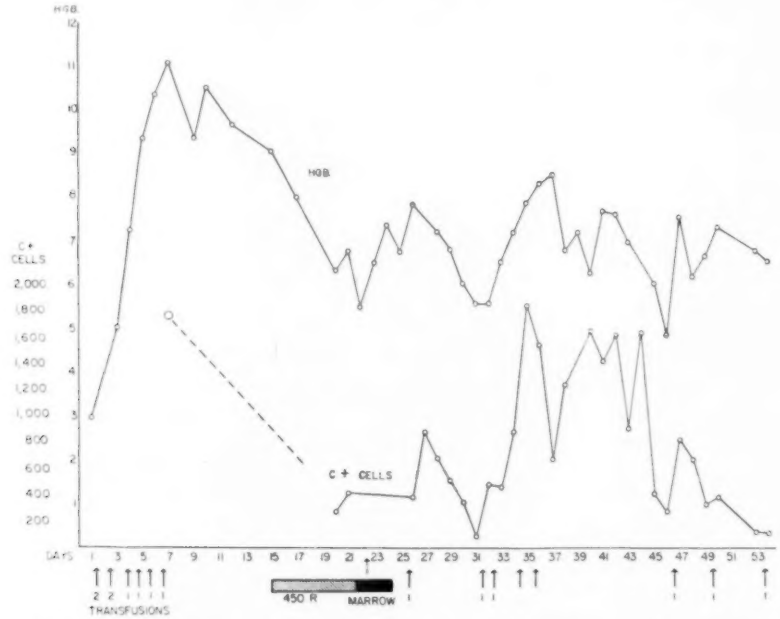

Fig. 8.—(Taken from **Thomas, E. D., Lochte, H. L., Jr., Lu, W. C.,** and **Ferrebee, J. W.:** Intravenous Infusion of Bone Marrow in Patients Receiving Radiation and Chemotherapy. New England J. Med., **257**, 491, 1957.)
C+ cells are plotted in thousands per cubic millimeter. It may be seen that from the thirty-fifth to the forty-third day more than half the circulating erythrocytes were C+

We come then to a summary of the factors to be watched in making a transition from rodents to large animals such as man and perhaps they may be summarized by looking at some recent work with dogs (Ferrebee *et al.*[16]).

Dogs do not respond well to marrow transplantation after large doses of radiation. They routinely die. This is unfortunate, for the dog is a popular animal for surgical procedures, and many transplantation techniques could be worked out and indeed have been worked out in this species as far as surgical details are concerned: heart, skin, kidney, lung transplants. It is known that after a radiation in the LD 100 range* (600 R), a dog can be made to recover if prior to radiation 1 or 2 billion of his own marrow cells are aspirated from ribs or pelvis and set aside for re-introduction immediately following radiation exposure (Alpen and Baum[1]). The difficulty seems to be that radiation in the range 600 to 900 R, which is the limit of intestinal tolerance, is not enough to eliminate immune mechanisms and let a marrow graft from another dog grow successfully. This is unfortunate, but may be turned to good account. In an animal in which it is difficult to make

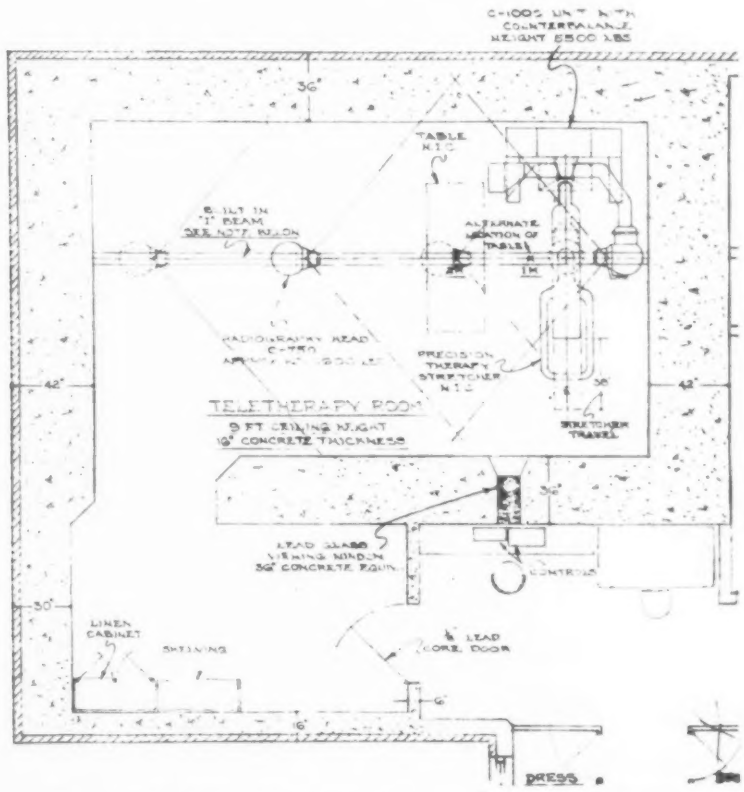

Fig. 9.—Cobalt-60 Teletherapy Unit for whole-body radiation.

*LD 100 = lethal dose all animals, LD 50 = lethal dose 50% of animals.

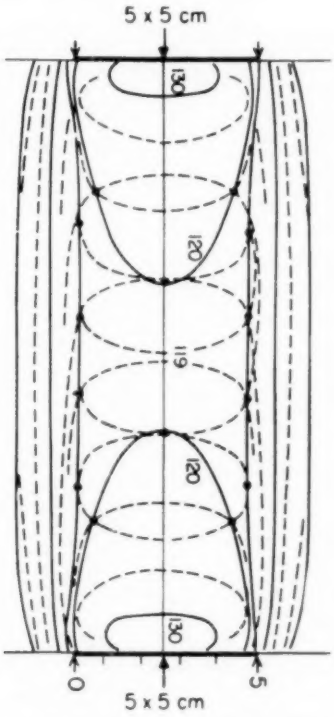

Fig. 10.—(Taken from **Johns, H. E.:** X-rays and Teleisotope γ-Rays. Radiation Dosimetry by Hine and Brownell, Chapter 12: 532–594. New York: Academic Press, 1956.)

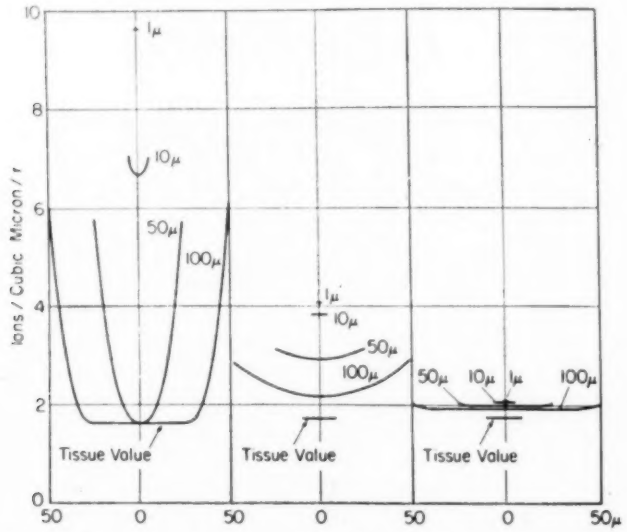

Fig. 11.—(Taken from **Spiers, F. W.:** Brit. J. Radiol., **22**, 521, 1949.)

a postradiative marrow graft work, important requirements may stand out in sharp relief. The dog, therefore, may be an excellent animal in which to study subtleties and tricks for getting this type of therapy to go in man, if man too turns out to be a difficult species.

Consider the details shown in Fig. 12. The essential point is that a properly prepared animal; a healthy, splenectomized male dog with lymphoid tissue reduced by chronic administration of ACTH, received an LD 50 of total body radiation on each of three successive days. Transfusion of a large amount (8.6 billion nucleated cells) of marrow from a closely related source (sibling female) then produced a successful graft and the dog lived. Dogs that were not splenectomized or given ACTH to reduce their immune responses, did not live; and dogs that received too little marrow, 2 to 4 billion cells from unrelated animals of different strain, failed to survive.

Repeated sublethal doses of Roentgen-ray have relatively more effect on lymphoid tissue and immune responses and relatively less effect on bone marrow and other tissues than do single large doses of radiation. This was pointed out by Murphy and Sturm[27] in 1925: "A Method for Destroying Lymphoid Tissue by X-ray Without Damage to Bone Marrow," and may be of present applicability. At least we

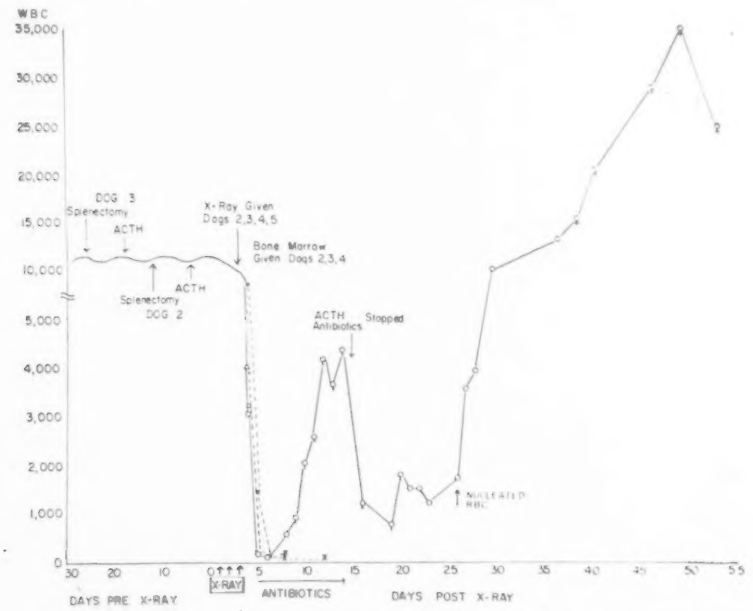

Fig. 12.—Peripheral leukocyte counts following lethal total body radiation and marrow transfusion in the dog. ♀ —female type polymorphonuclear cells present in the circulation of male dog #3. The notation "nucleated RBC" denotes a period when immature forms of red blood cells and white blood cells appeared in the peripheral circulation and when, because of immaturity, leukocytes of the female type could not be recognized. The dotted lines stopping on days 6 and 12 represent the course of the white blood counts in dogs 4, 5, and 2 respectively. (Taken from **Ferrebee, J. W., Lochte, H. L., Jr., Jaretzki, A. III, Sahler, O. D.,** and **Thomas, E. D.:** Successful Marrow Homograft in the Dog after Radiation. Surgery, in press.)

had it in mind when spreading out the radiation effects by using repeated LD 50 doses instead of a single LD 100 exposure. The use of ACTH and splenectomy as further means of reducing immune response is obvious. The importance of using genetically related donor marrow in large amount is also obvious when working with a species in which grafts do not take well. The device of following graft survival by persistence of leukocytes of the female type (Davidson and Smith[12]) seems satisfactory and induces no antigenic complications. The reverse, male into female, may (Eichwald and Silmser[14]), because of antigenicity associated with the unique male Y chromosome.

In conclusion then there would appear to be a number of variable factors controlling successful homotransplantation: closeness of genetic relationship, sex, reactivity of immune mechanisms and their alteration by embryologic, radiologic, and adrenal approaches. At each stage there are quantitative variants to be managed: age of embryo, intensity and duration of antigenic stimulus, total dosage and rate of dosage of radiation, size and duration of adrenal effect upon lymphoid tissue, quantity and efficiency of marrow used as seed to re-establish viability with altered immune response after lethal radiation of the entire body. Working with these variables, we may expect over a period of time to develop a mode of procedure that will permit in man the successful homotransplantation now demonstrated in animals.

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SUMMARIO IN INTERLINGUA

Factores Que Affice Le Superviventia De Histos Transplantate

Es presentate un revista del factores immunologic que affice le superviventia de histos transplantate. Duo major manieras de attaccar le problema de effectuar homotransplantationes a bon successo es discutite. Le un se basa super considerationes embryologic, le altere travalia con radiologia. Es considerate le problema de effectuar transplantationes successose de medulla ossee in humanos, insimul con le question de immagasinar medulla ossee e le methodos de su administration e etiam le technicas del evalutation *in vivo* e *in vitro* le successo de transplantationes de medulla in humanos. Le problema general del transplantation de medulla es illustrate per un studio in canes. Ab isto il es concludite que plure factores variabile determina le successo de homotransplantationes: Proximitate del relation genetic, sexo, reactivitate de mechanismos immunologic, e le alteration de illos per causas embryologic, radiologic, e adrenal. Ab omne iste punctos de vista il es necessari prender in consideration variantes quantitative: Etate del embryo, intensitate e duration del stimulo antigenic, dosage total e concentration del doses de radiation, magnitude e duration del effecto adrenal super le histos lymphoide, e quantitate e efficacia de medulla usate como semine pro restablir le viabilitate del organismo con alterate responsa immunologic post radiation letal del corpore integre. Per laborar con iste variabiles, nos pote expectar successo in disveloppar in le curso del tempore un technica pro le execution de efficace homotransplantationes in humanos como illos es nunc executabile in animales.

CUSHING'S SYNDROME PRODUCED BY NORMAL REPLACEMENT DOSES OF CORTISONE IN A PATIENT WITH DEFECTIVE MECHANISM FOR STEROID DEGRADATION*

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In considering disorders of the glands of internal secretion, physicians are accustomed to think in terms of overproduction of a hormone by hyperplasia or tumefaction of a gland, or in terms of underfunction secondary to atrophy or destruction. More recently with the plethora of hormonal products available, we see not infrequently iatrogenic (doctor induced) disorders, when excessive quantities of one or another of these compounds has been administered, mimicking quite exactly the spontaneously occurring clinical picture (as, for example, with thyroid, androgens or adrenal corticoids).

Less often have we thought of the possibility that something may have gone awry with the mechanism whereby the hormone is normally destroyed, inactivated or excreted. The following case represents, we believe, an example of an instance of this sort, in which a *normal* quantity of a *normal hormone* evoked the typical changes of a classical overproduction syndrome.

Case Report. CASE 1. J.H.H. #452636. A man of 43 had developed signs of acromegaly in early manhood. Twelve years previously he had received two courses of Roentgen irradiation to the pituitary for headaches, which, however, persisted. Five years ago, operation had been performed because of the headaches and the operative note states that only a small portion of the tumor was removed. There were no ocular abnormalities. The surgical intervention was followed by disappearance of the headaches, and for three years he felt well. Considerable recession of the general soft tisssue somatic enlargement had occurred. Three years after operation and 8 years after the last irradiation, Mr. M. began to feel weak, lost libido and potentia, often felt lightheaded and giddy. He appeared pale and had been treated for anemia. Coincident with a mild skin infection, weakness had greatly increased; and it was in another hospital that we first saw him in 1953.

The findings may be summarized with the statement that all the classical features of panhypopituitarism were evident. There were present pale dry skin, progeric wrinkling about the eyes, minimal facial, axillary and pubic hair, gonads small, prostate barely palpable, normal blood pressure, moderate normocytic anemia. Our note on that hospital record describes him as a pale, apathetic mass of protoplasm in an acromegalic frame.

Electrolyte pattern was not abnormal nor did erect posture produce fall in blood pressure, but steroid assays were very low, fasting glucose 50 mg., with a flat glucose tolerance curve. What was present on the hospital record, but did not register with us, was a normal serum total protein with a 1:1 A/G ratio and a 4 plus cephalin flocculation test. Cholesterol was 230 mg. per 100 ml.

*This paper was read at the annual meeting of the American Clinical and Climatological Association, held at Hot Springs, Virginia, October 28–30, 1957.

Advice was given for the patient to receive 30 mg. methyl testosterone per day and 25 mg. cortisone orally in divided doses. When we saw him 6 weeks later in brief consultation, the change was dramatic. He was alert, even overactive, had gained 25 lbs. from an appetite which his wife described as ravenous, and was rapidly recovering his generally hirsute state of several years back. Blood pressure was normal.

There was now another hiatus of 8 months before we saw the patient again at a single consultation visit. There had been a gain of 50 lbs. and weight was 200 (25 lbs. over his greatest previous weight). There were no complaints; indeed he was euphoric and boasted of being the strongest man at the steel plant in the tossing of ingots, statements verified later by his companions (in view of the situation later discovered, most extraordinary indeed). The distribution of his weight was not Cushingesque, but there were pink striae on the abdomen and hips, and blood pressure had risen to 210/110. No features suggestive of thyroid deficiency were present. We were distinctly puzzled by all this, but no further studies could be made.

In February, 1956 (*slightly more than two years after testosterone and cortisone therapy had been begun*), the patient came under our direct care and he consented to enter the hospital for study because he was having severe morning headaches. Weight was unchanged, but his face and neck had become fat; and arms and legs were spared. The striae were more conspicuous and now quite broad and red. Thyroid was very small, but there was no dryness of the skin, absolutely no cold intolerance and the patient sweated vigorously in the hot. Blood pressure was 210/115. Hemoglobin was normal. Cholesterol was 308 mg. per 100 ml. Diabetes was not present. The bones showed minor osteoarthritic changes but no rarefaction. There was no anemia; sedimentation rate was 34 mm. in half an hour. The following liver function tests were found abnormal: cephalin flocculation, 3 plus; thymol turbidity, 23 units; Bromsulfalein retention, 3.1 mg. per 100 ml. at half an hour. Total serum protein was 8 gm. per 100 ml., with albumin and globulin each 4 gm. Protein bound iodine was 1.3 micrograms and, after three daily injections of TSH (thyroid stimulating hormone), rose to 2.8 micrograms. Radioiodine tracer test showed an uptake slope of 0.13 which rose to 0.21 after 3 days of stimulation by TSH.

The clinical impression was that the patient had developed many of the symptoms and signs of hyperadrenocorticism despite the low dosage of only 25 mg. cortisone per day, that he had hepatic dysfunction of unknown cause, that there was laboratory evidence of striking thyroid underfunction with no clinical symptoms or signs of thyroid deficiency whatever, and that perhaps either the liver disorder or the hypothyroidism was responsible for the Cushing's syndrome by virtue of having impaired the patient's capacity to degrade cortisone in the usual manner.

One milligram hydrocortisone per kilogram of body weight was intravenously administered in alcohol and 250 ml. normal saline over a half-hour period; plasma levels of free 17-hydroxycorticosterone were determined over a 6-hour period. The curve proved to be decidedly abnormal.

TABLE 1.—LABORATORY DATA DURING TREATMENT NOTED

	Feb. '56	*May '56*	*Oct. '57*
Htct.	40	43	44
Chol.	308	—	287
C.F.	2+	3+	0
T.T.	20 U.	23 U.	5 U.
BSP	3.2 mg.	3.1 mg.	2.8 mg.
Alb.	4.0 gm.	—	3.8 gm.
Glob.	4.0 gm.	—	2.8 gm.
P.B.I.	1.3 micro.	6.1 micro.	—

To the patient's previous regimen there was now gradually added 2 grains thyroid USP per day, and testosterone therapy was changed to 300 mg. enanthate intramuscularly once per month.* No other changes were made. The patient returned for examination *three months* later, having lost 25 lbs. in weight (appetite had become much less) and commented that "all the weight loss seems to be from my face and neck and now I look like my old self again; I feel fine but couldn't feel better than before." The striae had faded markedly. Blood pressure had fallen to 150/90. Protein bound iodine was 6.1 micrograms, a normal level. Hydrocortisone degradation curve was now much more

*Since methyl testosterone is known to raise the basal metabolic rate, it was thought perhaps this drug might be the reason for the absence of some of the usual symptoms of thyroid deficiency. However, the change to depot testosterone was purely for the patient's convenience.

nearly normal. However the liver function tests had not changed an iota.

The regimen of cortisone, testosterone and thyroid was continued; and when seen *20 months* after thyroid had been started (2 weeks ago), the patient still felt entirely well. Striae were now pearly white; weight was 180 lbs.: his normal. Blood pressure was 150/90. Results of the laboratory studies may be seen in Table 1. Degradation of hydrocortisone was still abnormal (Fig. 1).

In February, 1956, patient had been on 25 mg. cortisone and 30 mg. methyl testosterone, both taken orally, each day for 2 years. At this time thyroid hormone was added, and depot testosterone (testosterone enanthate) 300 mg. i.m. once each month was substituted for the methyl testosterone. This regimen has been continued to date of writing.

In summary, a man with adrenal, gonadal and thyroid deficiency had, with usual doses of androgen and adrenal corticoid replacement over a 2-year period, developed signs of hyperadrenocorticism. Tests of liver function gave evidence of derangement of this organ. When thyroid replacement therapy was added but other medication continued unchanged, all the manifestations of Cushing's syndrome disappeared within 3 months. Disappearance rate of injected hydrocortisone from the plasma, slow prior to thyroid therapy, returned *toward* normal during treatment with thyroid hormone, but the

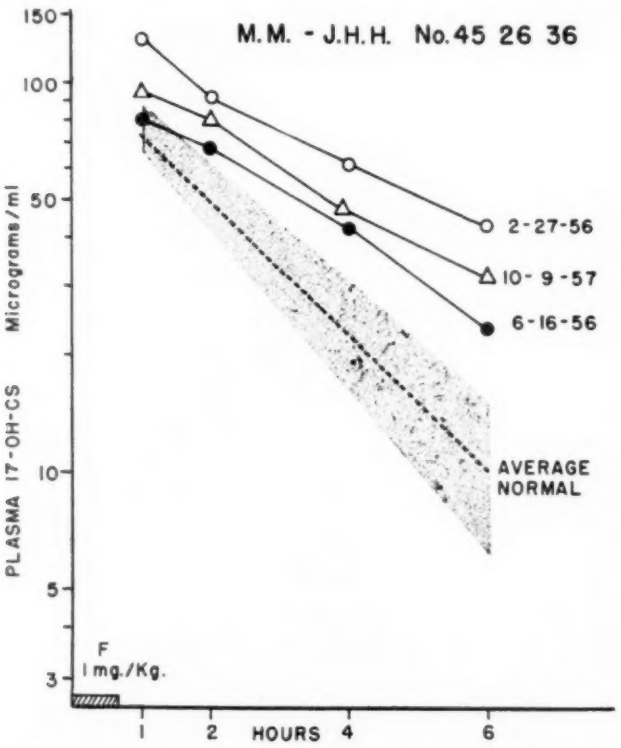

Fig. 1.—Gray area shows normal variation for degradation curve when 1 mg. hydrocortisone per kilo of body weight is injected intravenously. Degradation curves of patient M.M. are shown for comparison. On Feb. 27, 1956, patient was hypothyroid, with P.B.I. of 1.3 micrograms and had been treated for 2 years with methyl testosterone and cortisone. On June 16, 1956, P.B.I. was 6.0 micrograms and patient had been on thyroid 2 grains daily for 3½ months, other medications being continued. On Oct. 9, 1957, patient had been on same medication for 18 months.

abnormal tests of liver function: cephalin flocculation, thymol turbidity, BSP retention, elevated serum globulin concentration, remained unchanged. *After 20 months* of euthyroidism the liver function tests with the exception of BSP excretion, had become normal; but hydrocortisone degradation still remained slower than normal.

normalcy. Nevertheless, there was sufficient improvement so that classical and quite severe manifestations of hyperadrenocorticism disappeared while the dose of cortisone, considered to be the approximate equivalent of a man's daily normal output, was continued.

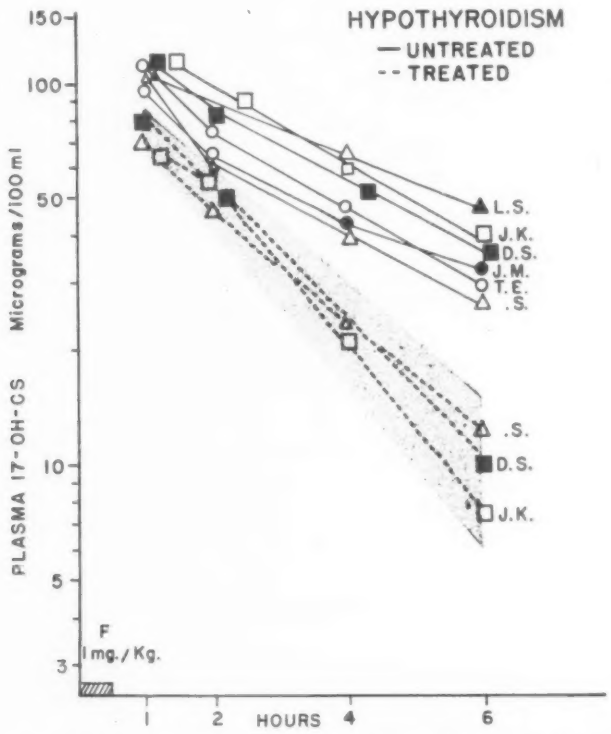

Fig. 2.—Hydrocortisone degradation curves on 6 patients with untreated hypothyroidism and of 3 of these patients after thyroid replacement therapy. Gray shaded area is the range shown by normal persons.

Discussion. There are many interesting features of the data available on this patient which warrant discussion and speculation, despite much that remains obscure. It would appear that there existed a defect in the mechanism for disposing of adrenal corticoids which replacement therapy with thyroid hormone affected favorably, though not reverting it to complete

The idea that the hypothyroid state is associated with a slower degradation of corticoids is not new. One of us found abnormal hydrocortisone degradation curves in 4 patients with hypothyroidism; 2 were retested after treatment and found to have reverted to normal[5]. Six cretins have been studied by Wilkins and Migeon with similar findings, and 2 of these were treated

and, when retested, were found to have a normal degradation curve (Fig. 2). Peterson[6] has published similar studies both before and after thyroid therapy. Levin and Daughaday[4] reported observations indicating a slowed rate of degradation of adrenocorticoids in hypothyroidism and an accelerated rate in thyrotoxicosis. Wilkins[7] has seen Cushing's syndrome develop in a 2½-year-old hypopituitary child who was taking only 15 mg. of cortisone per day. Yet Eik-Nes and Brizzee[3] found no change in the disposal of hydrocortisone in dogs, 7 and 30 days after thyroidectomy; it is possible, however, that a period of time longer than 30 days is required for the abnormal curve of hydrocortisone degradation to occur.

The hydrocortisone decay curve has been found to be abnormally prolonged also in patients with hepatic cirrhosis by Brown and colleagues[2]. The same authors believe that the defect in degradation of corticoids manifested by all these types of patients lies *not* in failure of conjugation but *is due to a block in the normal mechanism which transforms free hydrocortisone to the tetrahydroderivatives.* In a few instances,

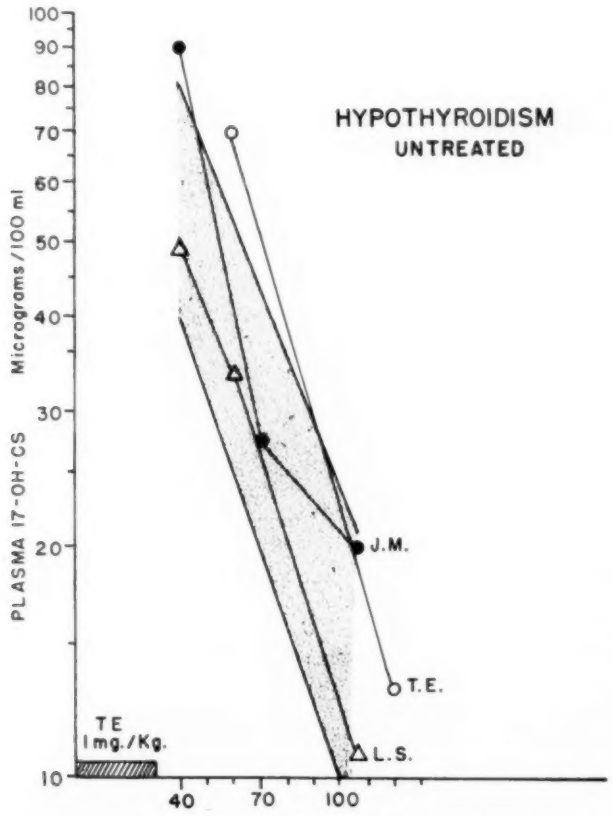

Fig. 3.—Degradation curves of 3 patients with untreated hypothyroidism after 1 mg. per kilo tetrahydrocortisone had been given intravenously. Gray shaded area demarks the variation in normal persons.

hypothyroid patients with abnormal hydrocortisone degradation curves have been given *tetrahydrocortisone* with perfectly normal response curves to this compound (Fig. 3).

When clinical signs of hyperadrenocorticism were evident in our patient, one might wonder whether the slower rate of hydrocortisone degradation was due to impaired liver function or to hypothyroidism, or to both. After 3 months of euthyroidism, the abnormalities of the liver function tests remained unaltered while clinical signs and hydrocortisone degradation curve indicated a return of the mechanism for disposal of corticoids toward the normal state. After 20 months of euthyroidism, liver function tests, with the exception of BSP excretion, had reverted to normal, but the hydrocortisone test was still somewhat abnormal.

It is difficult to explain these various findings in the light of our present knowledge, but we might speculate on this problem. Laboratory tests in our patient were consistent with cirrhosis of the liver (for which we never found any cause); it is, therefore, not surprising that the degradation rate of corticoids has not yet returned to normal. The requirement of adrenocortical steroids is known to be widely variable from patient to patient, and it is possible that a daily dose of 25 mg. of cortisone might not be sufficient for eucorticism in our patient if it were not for the slower degradation of hydrocortisone related to his liver dysfunction. When the patient was in a state of hypothyroidism, the same dose of cortisone was more than what was optimal at that time. This, however, is only one of several possibilities and is not a proven explanation.

Everyone who has seen many patients treated with adrenal corticoids is aware of the extraordinary variability with which the undesirable side effects (Cushing's manifestations) occur. From person to person there must be quite wide swings in capacity of disposal and degradation. It seems not unlikely that the reaction to stress may speed up disposal mechanisms and in this way increase the demand or need for these compounds which seems so clearly established on clinical grounds.

While speculating in this vein, one further comment perhaps deserves mention. In their report on hepatic cirrhosis in young females, from the Rockefeller Hospital, Bearn, Kunkel and Slater[1] report 3 out of 26 of these girls with clear-cut Cushing's manifestations. With *exogenously administered* hormone, one can readily visualize how a defect in degradation might produce a hyperadrenocorticism; but with *endogenously* produced hormone, one would have supposed that the normal homeostatic mechanisms would prevent overproduction by tamponading the release of ACTH and thus self-limiting the output from the adrenal cortices.

All of this bears food for thought and it may well be that we must now increase our visual horizon in considering both hyper- and hypofunctional glandular states. Enzymatic or other abnormalities in the mechanism for disposal of hormones may be the cause of some syndromes which we now call idiopathic.

Summary. A patient's case report is presented, in which panhypopituitarism occurred following hypophyseal operation for acromegaly. Under replacement treatment with androgen and cortisone 25 mg. per day orally, the patient developed many of the manifestations of hyperadrenocorticism (Cushing's syndrome). Thyroid therapy had not been given because there were no clinical evidences of hypothyroidism, despite the fact that radioiodine uptake and protein-bound iodine were in the hypothyroid range. Liver

function tests were also abnormal, there was elevated serum globulin, cephalin flocculation and thymol turbidity positive and Bromsulfalein retention was present.

With thyroid replacement (2 gr. USP per day) and the androgen and cortisone dosage being maintained, all manifestations of hyperadrenocorticism disappeared, before liver function tests returned to normal. No cause for the abnormal liver tests was discerned.

Disappearance rate of injected hydrocortisone was studied in the patient and, before treatment with thyroid, corresponded to those previously reported in patients with myxedema and with hepatic cirrhosis. Even when all evidence of hyperadrenocorticism had disappeared, hydrocortisone did not disappear at a normal rate in this patient.

The authors express the opinion that, in evaluating syndromes due to excessive quantities of a normal hormone, the factors of disposal of hormone should be given serious consideration. Where disposal mechanisms are interfered with, a normal quantity of a hormone may become a physiologically excessive quantity.

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(Interlingua on page 430)

CHRONIC AORTITIS OF UNDETERMINED CAUSE WITH SEVERE AND FATAL AORTIC INSUFFICIENCY*

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Since 1950 we have studied 5 patients with unusual aortic insufficiency characterized by rapidly progressive and fatal congestive heart failure. During life the etiology of the aortic insufficiency was unclear. In none was there clinical evidence of rheumatic fever, syphilis, subacute bacterial endocarditis, "pulseless disease" (Barker and Edwards[1], Ross and McKusick[13], and Trias DeBes *et al.*[14]), congenital heart disease, dissecting aneurysm, giant cell arteritis, or of rheumatoid arthritis. In one case the Marfan syndrome with aortic involvement was suspected from clinical study, but postmortem examination failed to confirm this diagnosis. In all 5 cases a striking form of aortitis was encountered at necropsy. The gross and microscopic alterations of the aorta were essentially identical in each case.

Case Reports. CASE 1. JC, a 22-year-old white woman, was admitted to the hospital on September 11, 1950.

History. Shortness of breath on exertion developed one year, and paroxysmal nocturnal dyspnea and orthopnea were present for 2 weeks, before admission. For 4 days there was cough, anterior chest pain and nausea. There was no history of rheumatic fever, but there was a history of scarlet fever in 1932. In April of 1940 she developed pain in her left chest and dyspnea. She was examined by Dr. R. W. Kissane of Columbus, Ohio, who discovered the signs of marked aortic insufficiency, slight enlargement of the left ventricle by roentgenogram, and a normal electrocardiogram. The Wassermann test was negative. Dr. Kissane made the diagnosis of rheumatic heart disease with aortic insufficiency.

Physical Examination revealed a pale, acutely ill young woman, with temperature 99.6° rectal, pulse 120, respiration 36, blood pressure 170/20.

Several small petechiae were noted in the conjunctivae. The external jugular veins were distended. Marked arterial pulsations were noted in the carotid arteries and all peripheral pulses were of the water-hammer type. The respirations were shallow and rapid but no rales were heard. The apical impulse of the heart was in the 5th interspace in the left anterior axillary line. A loud to-and-fro murmur was heard over the entire precordium but was maximal in the 3rd interspace to the left of the sternum and over the xyphoid area. The liver was enlarged 2 finger breadths below the right costal margin and was soft and slightly tender. The extremities showed no clubbing or cyanosis.

Laboratory Studies included: red cells, 4,450,000; hemoglobin 9 gm., hematocrit 30%, leukocytes 15,700, sedimentation rate 7 mm. per hour.

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A blood culture was negative as was also the Kahn test. The blood urea nitrogen was 51 mg. per 100 ml. An electrocardiogram showed sinus tachycardia and left ventricular hypertrophy.

Three million units of penicillin were administered and she was digitalized. Marked weakness persisted. The rectal temperature rose to 101°. On the day following admission, ankle edema was noted. On September 13, without warning, she suddenly expired.

Clinical Diagnosis: Rheumatic heart disease with aortic insufficiency. Subacute bacterial endocarditis?

NECROPSY: Cardiac hypertrophy. Signs of congestive heart failure. Lobular pneumonia.

Heart and Aorta: The heart was obviously hypertrophied and its left ventricle thickened. The aortic valve was thickened, its cusps shrunken and their margins rolled. Commissural separation was induced by intramural aortic fibrosis. Indicative of regurgitation, the subvalvular endocardium contained several horizontally disposed fibrous pockets and the columnae carneae were flattened. A photograph of the heart and aorta is shown in Plate 1, page 401.

Reflecting the severe degree of mural fibrosis and destruction of elastica, the aortic intima exhibited wrinkling, pitting and reddish brown discoloration. The wall was markedly thickened through the thoracic segment, a feature which ended abruptly at the level of the diaphragm and at the point of emergence of the various aortic branches. Certain of the microscopic changes are shown in Fig. 1.

CASE 2. GB, a 37-year-old colored woman, had four hospital admissions. The first was in November, 1949. At this time there was a one month history of epigastric pain and a one-year history of gaseous distention. The heart was enlarged and a loud to-and-fro murmur was described in the left 3rd interspace. The blood pressure was 140/40. An upper gastrointestinal roentgenographic study was negative. The Kahn test was also negative. A diagnosis of rheumatic heart disease with aortic insufficiency was made. The patient was admitted again in January, 1950, with complaints of boring epigastric pain and dyspnea. The heart rate was rapid but regular. Gallop rhythm was noted. Roentgenograms of the gastrointestinal tract were again negative. Roentgenographic and fluoroscopic studies of the heart revealed generalized cardiac enlargement with moderate enlargement of the left ventricle and left atrium. There was bilateral pulmonary congestion. The patient was digitalized and given mercurial diuretics. The third admission was in March, 1950, because of abdominal pain, nausea, vomiting and dyspnea. The pulse was 110, blood pressure 160/30–0. The liver was enlarged 4 finger breadths below the right costal margin. The spinal fluid Wassermann was negative. The final admission was in April, 1950. At this time there was nausea, vomiting, abdominal pain, tinnitus and dizziness. There was no venous distention, the heart was greatly enlarged and there was a to-and-fro murmur at the base. At the apex a systolic murmur and a low-pitched diastolic murmur were heard. Blood pressure 150/20–0. The peripheral vessels showed marked waterhammer type pulsations. There was no clubbing or cyanosis. Blood cultures were negative. Roentgenographic studies showed diffuse cardiac enlargement and pulmonary congestion. The course was progressively downhill. Death occurred on July 10, 1950.

Clinical Diagnosis: Rheumatic heart disease with aortic insufficiency. Subacute bacterial endocarditis?

NECROPSY: Heart weight, 580 gm. Hypertrophy of the left and right ventricle. Slight thickening of the tricuspid and mitral valves and slight shortening of the chordae tendinae of the mitral valve. The cause of death was congestive heart failure and lobar pneumonia.

Heart and Aorta: The heart was hypertrophied, weighing 580 gm. There was left ventricular thickening, the depth of the muscle being 16 mm. despite dilatation of the chamber. Slight thickening of the leaflets of the tricuspid and mitral valves was unaccompanied by evidence of incompetence. The aortic valve, on the other hand, had thin cusps but its commissures were spread as the result of nodular protrusion of the aortic intima at the points of insertion.

The aorta was identical with that observed in Case 1. Here, the coronary ostia were also displaced above the level of the valve leaflets but the arteries themselves were normal. Just above the aortic valve there was a shallow pouch-like dilatation of the aorta measuring 4.5 cm. in diameter and 1.0 cm. in depth. In the base of the aorta just above the aortic ring, there was a circumscribed area of coagulative necrosis with eosinophilic staining quality surrounded by a loose layer of reactive lymphocytes and histiocytes (Fig. 2). Although reminiscent of gumma formation, the lesion was not characteristically syphilitic.

CASE 3. BB, a 33-year-old colored man, was admitted to the hospital April 4, 1957, with the chief complaint of swelling of the abdomen. Three months before admission severe dyspnea developed on exertion. Ab-

dominal swelling occurred and during the month before admission orthopnea and paroxysmal nocturnal dyspnea appeared. Edema of the legs and abdominal swelling became progressively worse during the winter. There was chronic cough and three episodes of hemoptysis. There was no history of rheumatic fever or syphilis. He had been classified 4-F by the Army for unknown cause. Physical examination revealed a pulse of 100, blood pressure 160/80–50, and respirations 24. "probable anterior myocardial infarction." Roentgenography and fluoroscopy revealed cardiac enlargement with some tortuousity of the thoracic aorta. There was definite left atrial enlargement.

The patient was digitalized and placed on a strict cardiac regimen. After a 50-lb. weight loss, it was observed that his body stature was suggestive of Marfan's syndrome. There was a high arched palate. The arm span was 8" greater than his height and the pubis

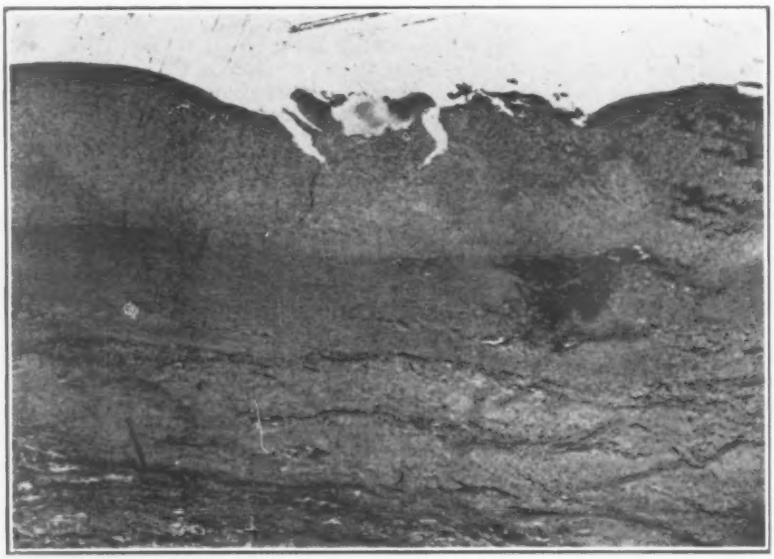

Fig. 1.—Enormous thickening of intima by edematous fibrous tissue. No lipid deposition. Erosion of intima with flaky fibrinous deposit. Poorly defined boundary between intima and media. Latter contains clusters of lymphocytes surrounding vasa vasorum. Low power magnification.

There was dullness of the lower chest bilaterally with diminished breath sounds. The apical impulse of the heart was in the 6th interspace in the left anterior axillary line. A Grade 4 harsh systolic murmur was heard at the aortic area and was transmitted to the carotid arteries. The systolic murmur was followed by a rough diastolic murmur transmitted along the sternal borders. The abdomen was tense due to ascites. The liver was enlarged 3 finger breadths below the right costal margin. There was massive edema of the lower extremities and of the genitalia. A VDRL test of the blood was negative. Three blood cultures were sterile. The electrocardiogram showed left ventricular hypertrophy and to foot measurement was 10" greater than the pubis to head measurement. The fingers were long and thin. There was no displacement of the ocular lenses. Paralysis of the left vocal cord was found, presumably due to left recurrent laryngeal nerve involvement. The patient was discharged May 20 and was followed in the cardiac clinic. He became progressively worse and was readmitted to the hospital July 11, 1957, in severe respiratory distress and with anasarca. The blood pressure was 130/40–0, pulse 116, with bigeminal rhythm. The peripheral pulses were of a water-hammer quality. There was marked distention of the neck veins. Acute pulmonary edema developed. Further digi-

talis was administered. However, severe respiratory distress continued despite all therapeutic efforts and he expired July 15, 1957.

Clinical Diagnosis: Marfan's syndrome with dilatation of the aorta and aortic insufficiency. (Nonspecific aortitis with aortic insufficiency was suggested by one physician.)

The noncoronary cusp, in this instance, had apparently been the seat of disruption at some time in the past and hung freely as a pocketed flap measuring 1.2 cm. in length and 0.6 cm. at its base in the attached end of the valve. Subvalvular endocardial ridges indicated regurgitation. The coronary orifices were displaced upward.

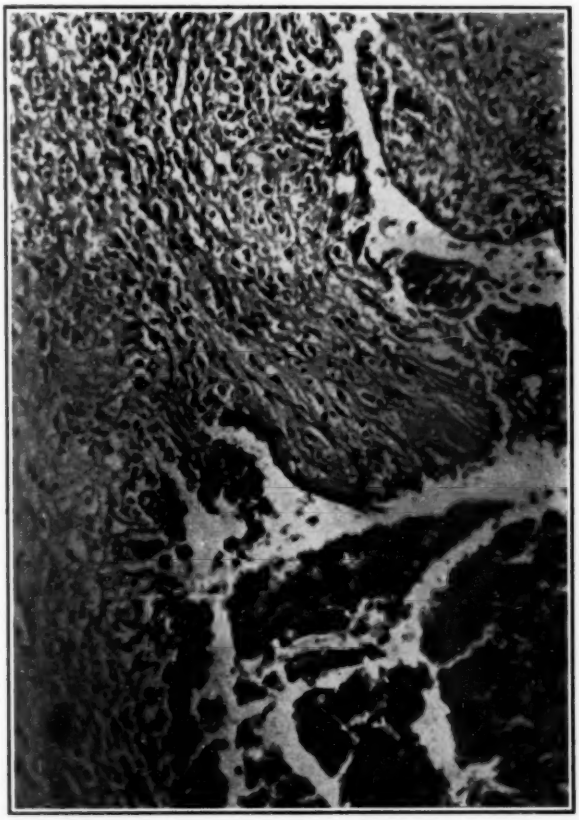

Fig. 2.—Microscopic section of base of aorta. A nodule of coagulation necrosis appears above aortic ring. This resembles changes ascribed to syphilis and recently described in rheumatoid arthritis.

NECROPSY: Heart weight, 655 gm. Cardiac hypertrophy and dilatation. Old infarcts, brain and kidney. Congestive heart failure.

Heart and Aorta: (Fig. 3) The heart was enlarged, weighing 655 gm., and the left ventricle was thickened (18 mm.). Only the aortic valve was abnormal. The two coronary cusps were shortened and thickened as in Case 1 and showed commissural spreading.

The wall of the entire thoracic aorta measured 0.9 cm. in thickness and was severely scarred. Again the process failed to continue into the abdominal aorta and major branches which were normal to microscopic examination. The nodular wrinkled intima and the widely destroyed media, which with elastic tissue stains had a moth-eaten appearance, resembled the aortas in the other 4 cases. As

in Case 2, a nodule composed of eosinophilic coagulative necrosis lay in the wall of the aorta just above the ring insertion.

CASE 4. GS, a 30-year-old white woman, became ill in July, 1956. There was no past history of rheumatic fever or syphilis and palmar erythema. There was low-grade fever. The sedimentation rate was 60. A blood culture at this time was sterile.

A diagnosis of rheumatic fever was made and penicillin, digitalis, and cortisone were given. There was no improvement.

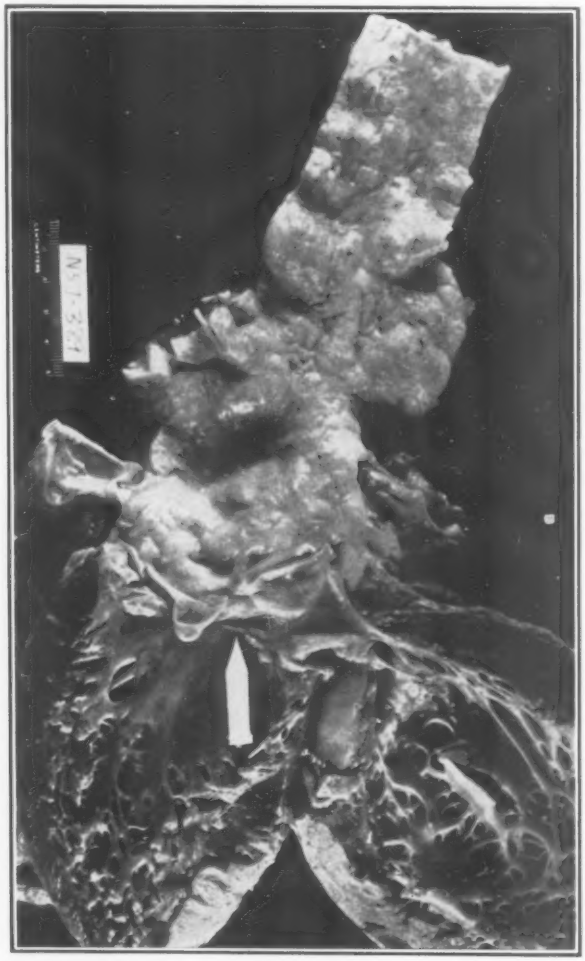

Fig. 3.—Thickened aortic valve margins; nodular fusion at commissures, disrupted cusp (see arrow). Thickened aorta with nodular thickening and wrinkling of the intima.

she had two normal living children. The complaints were aching pain in the left chest and shoulder. Physical examination revealed a to-and-fro murmur over the aortic area, a pericardial friction rub, tachycardia and diastolic gallop rhythm. The pulse pressure was wide; there was slight clubbing of the fingers and

She was hospitalized in September, 1956. At this time pallor was noted but there was no cyanosis. Temperature 98. The lungs were clear. The apical impulse of the heart was in the 6th interspace, beyond the midclavicular line. A to-and-fro murmur was heard maximally at the aortic area. A peri-

cardial friction rub was again noted. Blood pressure was 150/0. The liver was enlarged 3 finger breadths below the right costal margin but was not tender. There were marked peripheral signs of aortic insufficiency.

Laboratory Studies included: hemoglobin 14 gm., hematocrit 46%, leukocytes 10,500, sedimentation rate 32 mm. per hour, L.E. cell preparation negative, VDRL negative, 7 blood cultures negative, ASO titer 12 units, C-reactive protein 1+.

The electrocardiogram showed left ventricular hypertrophy.

Clinical Diagnosis: Rheumatic heart disdisease with aortic insufficiency. Superimposed subacute bacterial endocarditis? (One consultant suggested nonspecific aortitis with aortic insufficiency.)

NECROPSY: Embalmed specimen. Heart weight 450 gm. Dilatation of the ventricles. Slight thickening of mitral valve and of chordae tendinae. Pulmonary embolism.

Heart and Aorta: The heart which weighed 450 gm. resembled that seen in Case 1 save for mild thickening of the free margin of the mitral valve. The aortic valve and the aorta

Fig. 4.—Low power view of aorta stained for elastic tissue. There is marked fibrosis of the outer half of the media with flame-shaped disruption focally. A fibrin deposit lies upon the intima. The adventitia is densely scarred.

Roentgenogram of the chest showed moderate cardiac enlargement and a hazy infiltrate in both lung fields. The ascending aorta encroached upon the anterior clear space in the lateral view.

ACTH was administered with no improvement. A 4-week course of penicillin and streptomycin was then instituted. Despite this therapy the patient pursued a downhill course. On December 4, 1956, she suddenly experienced left chest pain and shock occurred. Roentgenogram of the chest and an electrocardiogram were consistent with the diagnosis of pulmonary embolism. She expired the same day.

were identical in appearance with those in Case 1.

Microscopic examination of the myocardium, in this instance, revealed an intense infiltration of the interstitial tissue by neutrophils. Indeed, the process bordered upon being suppurative in nature. The mural scarring of the aorta, the destruction of the elastica and the intramural vascular alteration (Figs. 4 and 5) were all exactly as encountered in Cases 1 and 2.

CASE 5. MW, a 15-year-old colored boy, was admitted to the hospital in acute respiratory distress. He had been in good health, according to his mother, until about 3 months

previously when he had begun to complain of a burning substernal pain and a sensation of "something pushing around his heart." At about the same time he had been sent home from school with a fever of 101°. He was kept in bed for one week, during which time he experienced shortness of breath but no cough. Shortly thereafter he experienced recurrence of the burning chest pain. One month prior to admission he was examined by a physician who stated that he had heart trouble and prescribed medication. His symptoms worsened, however, and for several weeks before admission he had been sleeping in a chair with his head resting on the window sill because he could not lie flat in bed. Two weeks before hospitalization he became worse and was unable to walk any appreciable distance because of shortness of breath and substernal burning. Three days before admission he had an episode of vomiting. His appetite had been good until about this time, although he had complained of aggravation of his chest pain when eating. About 3 A.M. on the morning of hospitalization he coughed up what was estimated to be 3 or 4 ounces of blood.

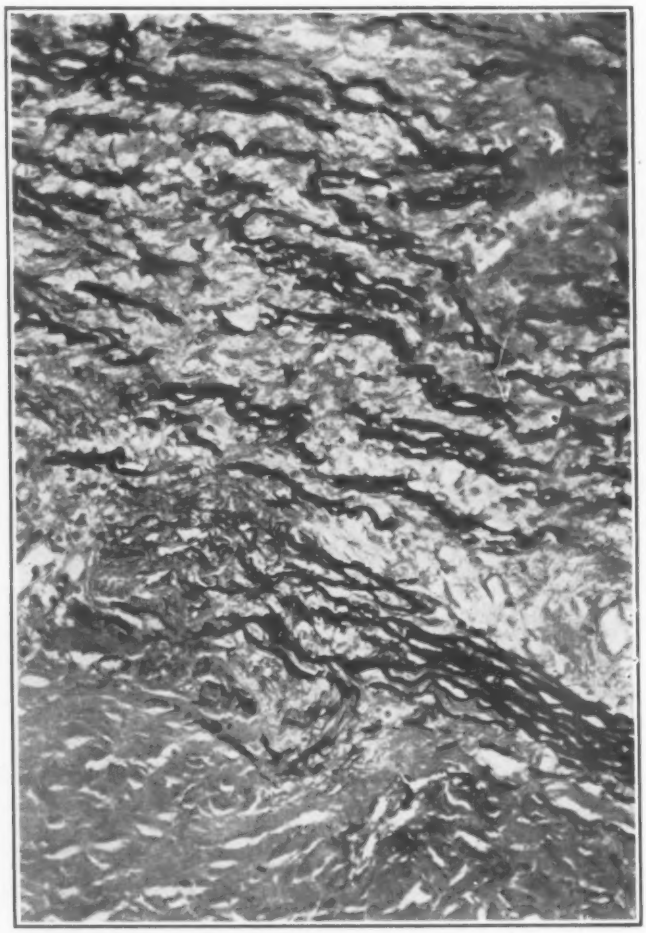

Fig. 5.—Elastic tissue stain of aortic media. High power view shows disruption and fragmentation of elastic fibrils separated by fibrous scar. Cicatricial adventitia below.

He had whooping cough as an infant, small

pox at the age of 6 years, chickenpox at 7, and measles at 8. There was no history of scarlet fever or rheumatic fever. His past history also included two previous periods of hospitalization. The first was at the age of 11 months for infantile eczema. One week following discharge he was readmitted because of bronchopneumonia. Examination at this time revealed no evidence of heart disease. The past history otherwise and the family history were noncontributory.

Physical examination revealed an acutely ill colored boy who complained of substernal and abdominal pain and with temperature 102° (R), respirations 30. The blood pressure and the pulse could not be obtained. He was dyspneic but seemed most comfortable lying flat in a hyperextended position. His face, mucous membranes and conjunctivae were pale and there was slight cyanosis. Blood was seen in his nose and there was blood which he had coughed up, in an emesis basin. His extremities were cold. There were scattered rales at both lung bases and in the right axilla. The heart was enlarged to the left, the rate was rapid (118/min.), with frequent premature beats. There was a short grade 2 systolic murmur at the apex.

A roentgenogram of the chest revealed cardiac enlargement, predominantly left ventricular. The greatest transverse diameter of the heart measured 14.6 cm. in a chest measuring 25.5 cm. There were bilateral densities in the lungs radiating from the hilar area in a butterfly pattern.

Laboratory Studies: The hemoglobin was 13 gm. The white blood count was predominantly neutrophilic. Because of the urgency of his condition, no further laboratory studies (including a serology) were done.

He coughed up several ounces of frothy bloody sputum, which was followed by a large emesis of coffee-ground material. He extended his head over the side of the bed, breathed quietly for a few minutes and then gave a few short coughs and ceased breathing.

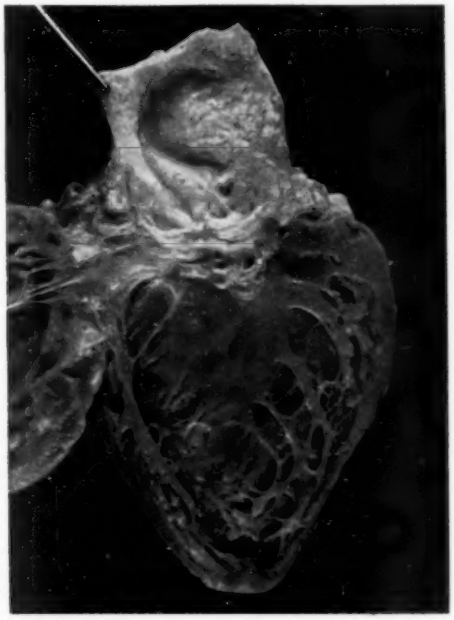

Plate 1.—The aortic wall is thickened, its intima wrinkled, and there is fusiform dilatation. A coronary orifice is displaced well above the sinus of Valsalva. The valve cusps are thickened, shrunken, and there is commissural separation. Secondary cusp formation is evident in the ventricular endocardium just below the aortic valve. Dilatation of the ventricle is accompanied by flattening of columnae carneae.

Clinical Diagnosis: Rheumatic heart disease. Congestive heart failure.

NECROPSY: Heart weight, 340 gm., occlusion left coronary ostium, focal myocardial infarction. Congestive heart failure.

Heart and Aorta: Moderate cardiac enlargement with dilatation primarily of the left ventricle. The aortic ring was not dilated (6.5 cm.) but the cusps were thickened, scarred and separated at the commissures. The proximal aortic intima for a distance of approximately 5 cm. had a nodular, puffy, pearly white appearance. The orifice of the right coronary was narrowed to 1.0 mm.; that of the left coronary was completely occluded by a fibrous plaque. Neither the coronary arteries nor the other aortic branches were affected. Several deep crevice-like scars penetrated the wall between the nodular thickenings. The upper ascending aorta and arch were entirely normal.

Microscopically, the aortic lesion was of the same general nature as that encountered in the other 4 cases but appeared to be of more active nature. The intima was identical in pattern. The thickened adventitia, however, was loose and edematous and the vascular channels here and in the media were the seat of active proliferative endarterial alteration. The tongue-like extensions of inflammatory exudate accompanying the vasa vasorum had a granulation tissue-like appearance. The elastica was the seat of extensive disruption and many sequestered bundles of smooth muscle and elastic tissue were undergoing fibrinoid degeneration and necrosis.

PATHOLOGIC FINDINGS. The pathologic lesions are herewith listed in composite fashion:

1. The lesion began in the base of the aorta and extended distally with abrupt cessation at, or immediately below, the diaphragm and at the points of emergence of the great vessels.

2. The aortic lesion was characterized by marked intimal thickening which reflected the irregular deposit of loose, edematous fibrillar connective tissue. This often assumed a noncircumscribed nodular character and imparted a peculiar salmon pink color to the wrinkled intimal surface. There was spotty superficial erosion with a flaky deposit of fibrin. Neither the intimal nor subintimal lesions were accompanied by significant cellular inflammatory exudate (Fig. 1).

3. The media was not sharply separable from either intima or adventitia. It exhibited wide but irregular destruction of elastica with replacement by collagen. Scarring was variable in intensity but often assumed a flame-shaped configuration (Fig. 4). Vasa vasorum were highlighted by perivascular collars of lymphocytes and the lumens of these vessels were narrowed as the result of concentric fibrillar subintimal thickening. The defect of elastica resulted in diffuse dilatation of moderate degree and more localized shallow pocket-like dilatations (Fig. 3).

4. The adventitia, too, was strikingly thickened and scarred. There was a high degree of vascularization by small arteries which were remarkable for their thickened walls, again in concentric fashion, and narrowed lumens. About many of these vessels were cuffs of lymphocytes.

5. In certain areas there was a more active inflammatory exudate in the media or the adventitia, or both. This was characterized by edema with loosening of fibrillar structure and an infiltration by lymphocytes and plasma cells. Histiocytes were not prominent and no multinucleated giant cells appeared.

6. In two of the cases, just above the aortic rings, there was a comparatively large though microscopic focus of coagulation necrosis resulting in a circumscribed but not encapsulated zone of brightly eosinophilic amorphous material surrounded by histiocytes and lymphocytes (Fig. 2). The former did not gather in tubercles or arrange themselves in palisade-like fashion.

7. The coronary ostia were uniformly displaced above the sinuses of Valsalva (Fig. 3), but the arteries themselves as in the case of the great vessels were not involved by the aortic lesion which

ceased abruptly as the vessel emerged from the aortic wall.

8. In one case the valve cusps were relatively normal although they showed commissural separation. In the other four the cusps were thickened and variously retracted. In one instance there was an old disruption of a cusp which hung loosely as a flap-like pocket (Fig. 3). The intima at the commissures was thickened and often caused separation of the cusps.

9. In the subvalvular region of the left ventricle there was a variable degree of intimal scarring, and in 3 instances horizontal ridge-like secondary or accessory cusps had formed.

The lesions in all 5 cases were identical, and indeed, superimposable. They were, moreover, very like those which have been described in aortic syphilis. In some respects they also resembled the aortitis which has been described in association with rheumatoid arthritis. They were, however, much more extensive and the histologic patterns more uniform.

Discussion. The clinical and pathologic study of these cases gives rise to the following questions:

Are these cases examples of acquired or congenital syphilis with negative serologic tests for syphilis? Is this the end stage of treated syphilis? Are these and similar cases in the past, considered as examples of syphilitic aortitis, the result of other etiologic agents?

The histologic and gross pathologic findings in each case closely resemble the characteristic alterations reported in syphilitic aortitis (MacCallum[1], Martland[6], and Yampolsky and Powel[16]). However, the lesions also resemble in some respects those encountered in the aortas of patients with rheumatoid arthritis (Clark, Kulka and Bauer[2], and Valaitis, Pilz and Montgomery[15]).

For the following reasons we question the etiologic role of syphilis:

1. There was nothing in the history to suggest syphilis.
2. The age range was young for syphilitic aortitis.
3. The serological studies were negative for syphilis in 4 cases and were not carried out in Case 5 because of the patient's sudden death shortly after admission.
4. There were no other stigmata of syphilis either clinically or pathologically.
5. For what it is worth, Levaditi stains for *Treponema pallidum* were negative.

Treponema pallidum immobilization or complement fixation tests were not carried out.

The statement of MacCallum[1] in connection with the discovery of Doehle and Heller of the relationship of aortitis to syphilis is of interest:

"Since then (1903) everyone has recognized it (syphilitic aortitis) at a glance except perhaps when it is very old and combined with arteriosclerosis. It seems one of those simple triumphs of observation that make one ashamed of having been so blind."

Perhaps we, too, have been overly influenced by the authority of the classical pathologic picture of syphilitic aortitis to consider the possibility that the end result of other etiologic agents may have caused similar and in fact identical responses in the aortic wall.

Mallory[5] in discussing 2 cases of aortitis in the case records of the Massachusetts General Hospital in 1936, made the following statement:

"It is not impossible that some of these as yet unclassified processes may produce lesions indistinguishable from syphilis. In each case the anatomic lesion is typical of the acute stage of luetic involvement of the heart which for two generations has been considered pathognomonic yet a significant number of arguments can be marshalled against such a diagnosis." It is of interest that these cases were in-

cluded many years later by Clark, Kulka and Bauer[2] as examples of arthritis.

None of our cases presented evidence either clinically or pathologically of rheumatoid arthritis or spondylitis. The 5 cases do not resemble, pathologically, other well recognized forms of aortic wall disease such as Takayashu's disease (Barker and Edwards[1], Ross and McKusick[13], and Trias DeBes, Sanchez Lucas and Gallesta Barcons[14]), aortitis due to rheumatic fever (Pappenheimer and Von Glahn[11,12]), giant cell aortitis (Gilmour[3] and McMillan[9]), cystic medial necrosis of the aorta (Moritz[10]) or Marfan's syndrome (Marvel and Genovese[7] and McKusick[8]).

The purpose of this report is to suggest that cases resembling luetic aortitis may be the result of other causes and a search for the etiologic agents may prove rewarding. In our 5 cases the causative agent was not determined.

Summary. (1) The clinical and pathologic findings in 5 patients with chronic aortitis and aortic insufficiency with a rapidly progressive and fatal course have been reported.

(2) The lesions resembled those encountered in syphilitic aortitis but there was no other clinical or pathologic evidence for syphilis and the existence of this disease in these patients seems doubtful.

(3) The probability that the aortitis was caused by an unknown etiologic agent other than syphilis is proposed.

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SUMMARIO IN INTERLINGUA

Aortitis Chronic A Causa Indeterminate, Con Sever E Mortal Insufficientia Aortic

1. Es reportate le constatationes clinic e pathologic in 5 patientes con aortitis chronic e insufficientia aortic a progresso rapide e termino mortal.

2. Le lesiones resimilava illos incontrate in aortitis syphilitic, sed nulle altere indicio clinic o pathologic de syphilis esseva presente, e le existentia de iste morbo in iste patientes es dubitose.

3. Es proponite como probabile que le aortititis esseva causate per un non-cognoscite agente etiologic altere que syphilis.

EFFECT OF BETA-SITOSTEROL ON SERUM CHOLESTEROL AND LIPOPROTEIN LEVELS OF PATIENTS INGESTING A LOW-FAT DIET

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The frequent association of elevated serum cholesterol and beta-lipoprotein levels with atherosclerosis has been repeatedly documented (Katz and Stamler[9]). This relation is seen not only in diseases in which atherosclerosis is a common complication, such as diabetes mellitus, myxedema, and various disorders of lipid metabolism, but also in many coronary artery disease patients, whose only manifestation of disturbed fat metabolism is the presence of slight to moderate elevations of blood lipids (Gofman *et al.*[6]). Keys and coworkers have demonstrated, in several populations, a direct relation between serum cholesterol levels, the proportion of fat in the diet, and the incidence of atherosclerosis[10]. Their studies infer that reduction in dietary fat will lead to a fall in plasma lipid levels, and may retard the atherosclerotic process.

Many studies have demonstrated that reduced intake of fat does indeed lower serum lipid levels in most patients, but to a variable, and not altogether predictable, degree (Newborg and Kempner[13]). Frequently, severe fat restriction is required to bring about a significant lowering of these blood constituents. Such a therapeutic regimen is difficult for the patient to maintain over long periods of time because of its unpalatability. Less demanding measures have been employed to lower blood lipoprotein concentrations, and presumably retard atherosclerosis, among them being the administration of large amounts of plant sterols. These materials are believed to block the absorption of ingested cholesterol, and impair the reabsorption of biliary cholesterol (Hernandez *et al*[7]). Several studies have indicated that this can be a highly effective means of reducing plasma cholesterol and beta-lipoprotein levels (Best *et al.*[2], Farquhar, Smith and Dempsey[4], Joyner and Kuo[8], Petersen[14] and Sachs and Weston[15]). In a few instances, this regimen has not been successful (Friedman, Homer and Byers[5] and Wilkinson *et al.*[17]).

It was recently shown in our labora-

tories that, in patients with atherosclerosis, S_f 0–12 serum lipoprotein levels are influenced by the fat content of the diet independent of body weight changes, whereas S_f 20–400 serum lipoprotein levels vary with changes in body weight[16]. The lowest concentrations of beta-lipoproteins were observed when patients ingested a low-fat diet which contained calories sufficient to maintain their reduced weight. The diet consisted of approximately 50 gm. of fat per day, a moderately strict low-fat regimen, but one to which patients had little difficulty adjusting. It was believed such a population, on the restricted diet, and maintaining approximately lean body weight, represented an excellent group in which further attempts to reduce blood lipids by the administration of sitosterols might be made.

Methods and Materials. Twenty-one male patients were studied. All had proven atherosclerosis, 18 having sustained one or more myocardial infarctions. The remaining 3 had severe atherosclerosis with arterial insufficiency of the lower extremities. Their ages varied from 34 to 63 years. The average age was 46 years; 8 were below the age of 40. All patients were followed in the Cardiovascular Clinic, Brooke Army Hospital. All patients had recovered from the acute phase of the disease and had been maintained at a relatively lean weight on a low-fat diet (below 50 gm. per day) for a prolonged period prior to initiating the present study. Eight of the patients had participated in a previous experiment indicating independent responses of serum lipid levels to both weight reduction and reduction of animal fat in the diet[16]. Patients' weights were maintained at constant levels and their diets remained unchanged throughout the period. All blood samples were taken in the fasting state. Initially, each individual had 2 control determinations taken at intervals of at least one week. Following the second control determination, patients were started on either one tablespoonful (16 ml.) of a 20% suspension of beta-sitosterols* or an equal dosage of a similar placebo lipid suspension. Medication was taken immediately before each meal. Patients received each preparation for a period of 8 weeks. Whether the placebo or the beta-sitosterol was received during the initial 8 weeks was determined by random selection and was unknown to the physician caring for the patient. Blood samples were taken at 2-week intervals so that 4 determinations were made during the administration of sitosterol and 4 during the administration of the placebo. Following completion of the study, another final control was taken 2 weeks after all medication had been discontinued.

Lipoprotein determinations were performed at the School of Aviation Medicine, USAF, Randolph Air Force Base, Texas. Standard S_f 0–12, 12–20, and 20–400 classes of beta lipoproteins were determined on each specimen[11,12]. Serum cholesterol determinations were done in the clinical laboratory at Brooke Army Hospital, Fort Sam Houston, Texas. The data were analyzed by M. Bryan Danford, Ph.D., Analytical Statistician, School of Aviation Medicine, USAF, Randolph Air Force Base, Texas.

Results. The mean serum lipid values during the various phases of the study are indicated in Table 1. Sitosterol administration resulted in highly significant reductions in the S_f 0–12 and S_f 12–20 serum lipoprotein fractions, as compared with placebo, and a probably significant reduction in the S_f 12–20 lipoprotein fraction, as compared with the initial control period. (The absence of highly significant differences between values of the sitosterol period and those of the initial and final control periods may be due at least in part to the fewer numbers of observations in these control periods.) There were no significant changes in either the serum S_f 20–400 lipoprotein levels or the serum cholesterol levels in any of the observation periods.

Table 2 details for each subject the per cent change in the blood lipid moieties during sitosterol administration as compared with the combined control periods. The combining of data from the 3 control periods was per-

*"Cytellin" provided through the courtesy of the Lilly Laboratory for Clinical Research, Indianapolis, Indiana.

TABLE 1.—LIPOPROTEIN AND CHOLESTEROL MEANS (± S. E.) IN 21 PATIENTS DURING TREATMENT PERIODS

	Periods			
No. analyses per subject/period	*Initial Control* 2	*Sitosterol* 4	*Placebo* 4	*Final Control* 1
Mg./100 ml.				
S_f 0–12	480 ± 18.2	447 ± 13.2	500 ± 13.2	496 ± 26.3
S_f 12–20	54 ± 3.8	42 ± 2.7 °°	54 ± 2.7	53 ± 5.4
S_f 20–400	134 ± 12.7	125 ± 9.0 °	145 ± 9.0 °°	156 ± 17.9
Cholesterol	312 ± 8.1	294 ± 5.8	302 ± 5.8	287 ± 11.5

°° $P < .01$
° $.05 > P > .01$

TABLE 2.—PER CENT CHANGE IN SERUM CHOLESTEROL AND LIPOPROTEINS OF PATIENTS TREATED WITH SITOSTEROL

	Subject Number	*Variable*			
		S_f 0–12	*S_f 12–20*	*S_f 20–400*	*Cholesterol*
Placebo First	1	−29.19	− 9.69	−23.43	−20.77
	2	− 3.27	−31.28	−53.98	− 3.23
	3	3.59	− 1.53	50.84	− 5.63
	4	6.38	−28.57	− 8.46	3.55
	5	− .93	−15.60	−28.02	−10.69
	6	−23.08	−23.96	−50.31	−13.08
	7	−29.49	−58.73	−41.09	21.19
	8	3.84	26.67	36.36	− 6.41
	9	−41.92	−42.71	−35.92	31.43
	10	− 3.12	−38.60	− 3.22	−11.13
Sitosterol First	11	− 6.22	−29.78	30.70	3.38
	12	− 2.49	−17.87	− 9.25	− .73
	13	3.62	47.48	2.11	9.50
	14	2.44	−21.19	− 1.72	−14.99
	15	−17.12	−26.03	21.00	−17.23
	16	−14.75	−29.97	−17.94	16.86
	17	14.81	−10.27	− 6.36	−19.83
	18	5.71	−37.93	7.43	−12.87
	19	− 9.85	−31.62	4.95	− 6.48
	20	−12.10	5.19	16.03	− 2.74
	21	− 2.84	−18.32	−28.65	− 5.62
Mean ($\bar{x}$)		− 7.43	−18.78	− 6.62	− 3.12
Standard deviation $\hat{\sigma}$		14.18	23.63	28.13	13.63
Standard error of the mean $\hat{\sigma}(\bar{x}) = \hat{\sigma}/\sqrt{21}$		3.09	5.16	6.14	2.97

formed as a convenient method of presentation after statistical analysis demonstrated this was a valid condensation. Analysis of the data in this form again revealed significant reductions only in the quantities of S_f 0–12 and S_f 12–20 lipoprotein moieties during sitosterol administration. The variability of the sitosterol effect among individuals is quite marked. If a change greater than 20% is arbitrarily chosen as a clinically significant alteration in serum lipid levels, then only 4 of 21 individuals demonstrated this mean reduction of the S_f 0–12 lipoprotein fraction on sitosterol therapy, while none showed a comparable elevation. For S_f 12–20 lipoproteins, 12 patients exhibited this reduction, while 2 had a similar rise. For the S_f 20–400 lipoprotein species, 6 showed mean decreases greater than 20%, while 4 manifested elevations of this extent. Finally, mean reductions of serum cholesterol greater than 20% occurred in only one subject, whereas a comparable rise occurred in 2 individuals. No significance to the arbitrary 20% change is intended, though certainly effects much smaller than this could hardly be construed as important in view of the known variability of blood lipid levels in the same individual at different times under manifestly similar circumstances.

Discussion. The effect of beta-sitosterol on serum lipoprotein levels parallels the action of a low-fat dietary regimen observed in a previous study[16]. Sitosterol presumably exerts its action by inhibiting the esterification and subsequent absorption of dietary cholesterol, and possibly inhibiting the reabsorption of biliary cholesterol (Deuel[3]). Since the amounts of animal fat and cholesterol in the diet are generally proportional, and fat in the diet is essential for the efficient absorption of cholesterol (Deuel[3]), a low-fat diet may also act, at least in part, by reducing the absorption of exogenous, and possibly biliary, cholesterol. Thus, the effects of these 2 regimens might be similar and to some extent, additive.

The lack of influence of beta-sitosterol administration on serum cholesterol levels is in contradistinction to the majority of clinical reports in the literature (Best *et al.*[2], Farquhar, Smith and Dempsey[4], Joyner and Kuo[8], and Sacks and Weston[15]). This might be explicable on the basis of the varied dosages employed in different studies. The amount of sitosterol ingested daily in this study was approximately 10 gm. Several workers have indicated this dose is about the minimum required to produce significant blood lipid changes. Above this dose, the effect is reported to be proportional to the amount administered (Barber and Grant[1], Joyner and Kuo[8], and Sachs and Weston[15]). The present observations thus indicate that changes in S_f 0–20 classes of beta-lipoproteins may be a more sensitive index of the efficacy of a sitosterol regimen. Since no toxic effects attributable to the drug were noted in this study, increasing doses to tolerance might be employed in an attempt maximally to depress blood lipid levels with beta-sitosterol.

It should be mentioned that depression of blood lipid levels by either dietary or drug regimens does not *a priori* mean that the effects on atheromata will be beneficial nor that the clinical course of atherosclerotic patients will be improved. Nor does it mean different regimens will have like effects on the disease process, though their influence on blood lipids is similar. Only prolonged studies of treated and control patients can finally determine if the atherosclerotic process is favorably influenced by such means.

Summary. Twenty-one male patients with overt atherosclerosis whose weight had been reduced to "lean"

levels and who were ingesting a low-fat diet, were given beta-sitosterol in a double-blind study. The drug was given over an 8-week period, and was either preceded or followed by a similar period of placebo administration. Though there was considerable individual variation in response to the drug, beta-sitosterol administration did result in significant reductions in mean levels of serum lipoproteins of the S_f 0–12 and S_f 12–20 classes. Changes in S_f 20–400 lipoprotein and serum cholesterol levels were not significant. The similarity of these blood lipid responses with those occurring on a low-fat diet regimen indicates similar mechanisms may be operative, and that these means of reducing blood lipid levels may be, to some extent, additive. No toxic effects were observed from the daily oral dose of 10 gm. of beta-sistosterol over the 8-week period. The results indicate beta-sitosterol has a definite effect in further lowering at least some species of serum beta-lipoprotein in patients whose lipid levels have already been reduced by dietary means.

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EFFECT OF PREFEEDING ON THE ACUTE RESPONSE TO LIPID MOBILIZER HORMONE IN MAN*

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A series of studies dealing with a new lipid mobilizing hormone (LM) have been reported from these experimental and clinical laboratories[6-15]. This substance was first discovered by Seifter and Baeder[6,7] who demonstrated its presence in the plasma of man, horses, dogs, and rats. More recently, these workers have isolated LM from the posterior pituitary gland of hogs[9]. The active principle has been crystallized and shown to be a peptide[10]. Most of the clinical and laboratory work with LM, however, has been performed with dialyzates of plasma from horses that have been pretreated with cortisone. Such treatment greatly increases the LM content of plasma, as do conditions of stress, including starvation. It was found that the injection of LM into fasting patients who were suffering from serious clinical disorders was followed by a prompt and striking increase in the plasma cholesterol, fatty acids, and lipid phosphorus (Steiger *et al.*[12] and Zarafonetis *et al.*[13]). Sustained hyperlipemia has also been elicited by daily injections into patients being maintained on a diet very low in fat content (Zarafonetis *et al.*[14]). On the other hand, non-fasting subjects and patients on a high fat diet have not shown a response to intravenous injections of LM (Zarafonetis *et al.*[14]). These latter observations suggested that the blocking effect of prefeeding might not be due simply to the total caloric intake alone, but rather to a specific food class. For this reason, it was decided to investigate the effect that prefeeding with a meal of carbohydrate, fat, or protein might have on the acute response to LM. The observations made in this connection form the basis of the present report. In addition, these studies include some results obtained in humans with the purified crystalline LM hormone.

Materials and Methods. Seven subjects were selected for study from the medical wards and Hematology Clinic of the Temple University Hospital. The principal criteria for inclusion in the study were patient cooperation and availability for the sequence of

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tests. The age, sex, weight, and clinical diagnoses of these patients are listed in Table 1. The plasma lipid response of each subject was determined, respectively, to: (1) an injection of LM alone, (2) an experimental meal alone, and (3) an experimental meal followed in 2 hours by an injection of LM. For each phase of the tests, the subject was fasted overnight from 6 P.M. the preceding day and throughout the following morning except as modified by the test feedings. In each case after a test procedure involving the administration of LM, an interval of 3 days was permitted to elapse before the next test was undertaken.

1. TESTS WITH LM ALONE. This was performed in all 7 subjects as follows: Base-line blood specimens were drawn after approximately 15 hours of fasting, and the subject was given an intravenous injection of LM. Plasma cholesterol, fatty acids, and lipid phosphorus determinations were made on the base-line specimens and on blood samples taken 1, 2, and 4 hours after injection of LM.

Two forms of LM were used in these experiments. One was the crude dialyzate of plasma from cortisonized horses[6,7]. It was administered intravenously in a dosage of 5 mg. per kg. of body weight. The other form of LM was the pure crystalline substance[10], of which a total of only 1.2 micrograms was administered for any given test.

2. TESTS WITH EXPERIMENTAL FEEDINGS ALONE. The plasma lipid changes following a fat meal were determined in 3 subjects, after a carbohydrate meal in 3 subjects, and after a protein meal in 2 patients. One subject (G.B.) was used twice, being tested with both carbohydrate and fat meals. Because of the acute nature of the experiment, cream was employed as the fat meal, glucose as the carbohydrate, and an aminoacid mixture as the protein feeding.

The fat meal consisted of 180 ml. of 40% cream, thereby providing approximately 72 gm. of fat. Analysis revealed the cream to contain 250 mg. per 100 ml. of cholesterol, of which 38 mg. was free, and 212 mg. was esterified; 3.0 mg. per 100 ml. lipid phosphorus; and a very large amount of fatty acids (over 10,000 mg. per 100 ml.).

The carbohydrate meal was 100 gm. of glucose, prepared and administered in the conventional method used for oral glucose tolerance tests.

The amino acid feedings consisted of a mixture of amino acids (Stuart's) dissolved in water. This is a total hydrolysate of casein which is fortified with tryptophane. Its approximate analysis is said by the manufacturer to show not less than 12.5% total nitrogen, and not less than 10% alpha amino acids. One subject received 85 gm. of this material as a test meal, and the other, 65 gm.

3. TESTS WITH EXPERIMENTAL FEEDINGS FOLLOWED BY LM INJECTION. The above experiments were repeated subsequently, with the subject receiving the same test meal as before. This time, 2 hours after ingestion of the test meal, LM was administered intravenously, and the plasma lipid levels were determined over the ensuing 4-hour period.

The methods used for cholesterol, lipid phosphorus, and fatty acids have been previously described[12,14]. Plasma amino acid nitrogen was determined by the method of Hawk, Oser, and Summerson[4].

TABLE 1.—EFFECT OF PREFEEDING WITH INDICATED FOOD CLASS ON HYPERLIPEMIC RESPONSE TO INTRAVENOUS ADMINISTRATION OF LM IN 7 SUBJECTS

					Hyperlipemic response from injection of LM:			
					a. fasting	*b. after prefeeding with*		
Patient	*Age*	*Sex*	*Wt. (Kg.)*	*Diagnosis*		*carbohydrate*	*fat*	*protein*
G.B.	50	F	47	Chronic granulocytic leukemia	yes (2)	blocked	blocked	—
J.Wi.	28	M	50	Sickle cell anemia	yes	—	blocked	—
J.We.	58	M	50	Cerebral vascular accident	yes	blocked	—	—
D.Wi.	56	M	90	CVA with uremia	yes	blocked	—	—
J.McQ.	38	M	77	"Low back syndrome"	yes	—	—	yes
H.S.	23	M	82	Severe head injury	yes	—	—	yes
A.M.	65	F	45	CVA	yes	—	blocked	—

Results. As can be seen in Table 1 and Figs. 1 to 7, all 7 subjects exhibited

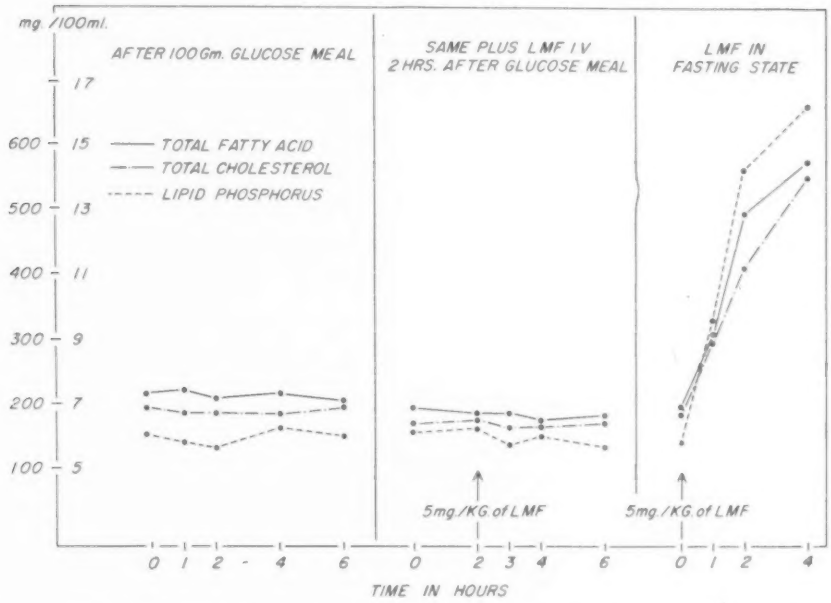

Fig. 1.—Plasma lipid levels of D.W., 90 kg. Negro male, with cerebral vascular accident and uremia. It can be seen that no significant change in lipid values occurred after a glucose meal (left) or after a glucose meal and an injection of the dialyzate containing LM hormone (center). This subject's response to LM when fasting is quite striking, however (right).

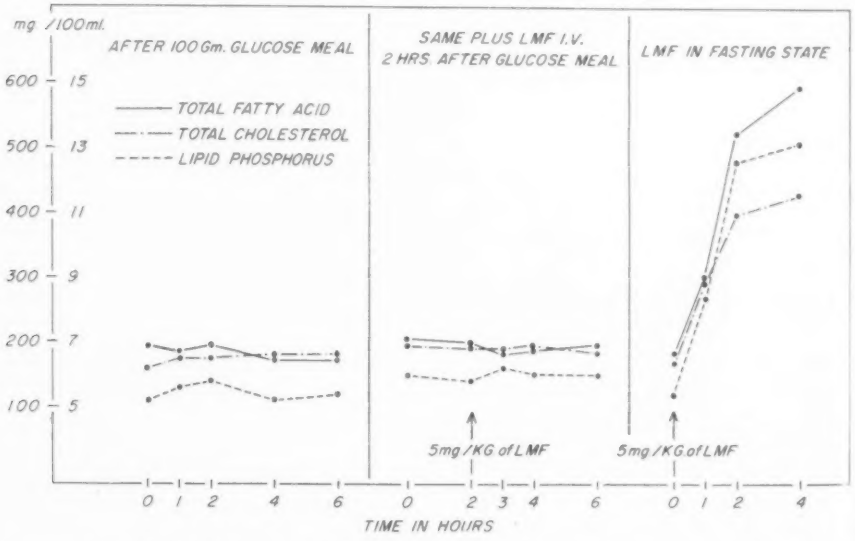

Fig. 2.—Plasma lipid levels of J.W., 50 kg. Negro male, with cerebral vascular accident during same sequence of tests with glucose feedings and LM as in Fig. 1.

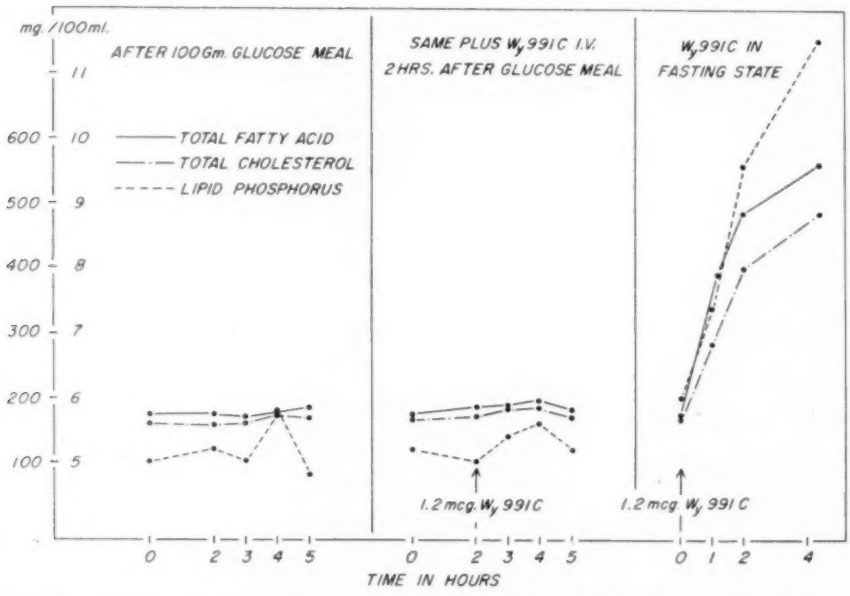

Fig. 3.—Plasma lipid values of G.B., a 48 kg. Negro female with chronic granulocytic leukemia, during same sequence of tests as in Figs. 1 and 2. The crystalline form of LM (Wy 991 C) was employed in the tests on this subject.

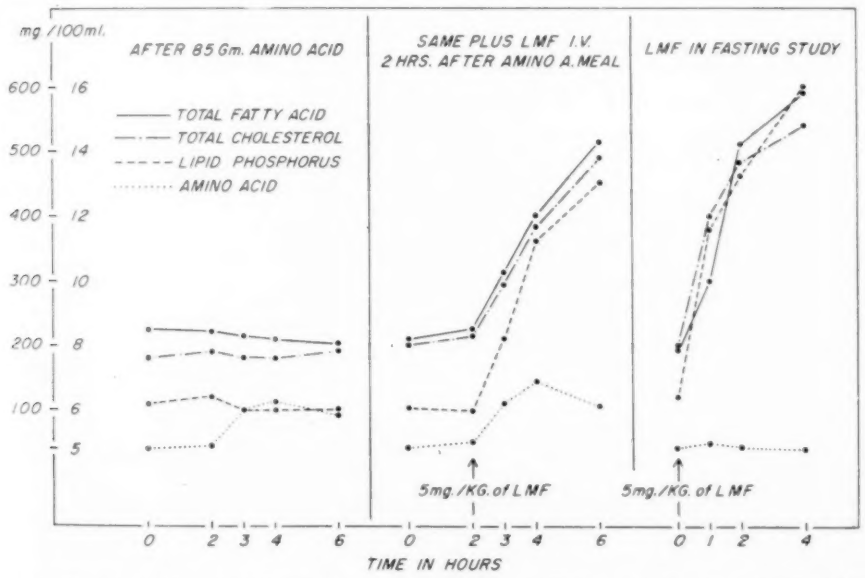

Fig. 4.—Plasma lipid and amino acid values of J.McQ., a 77 kg. white male with "low back syndrome." The patient's response to LM when fasting is shown in the panel at the right. Meals consisting of 85 gm. amino acids resulted in no change of plasma lipids (left panel), and did not prevent the hyperlipemic response to LM (center panel).

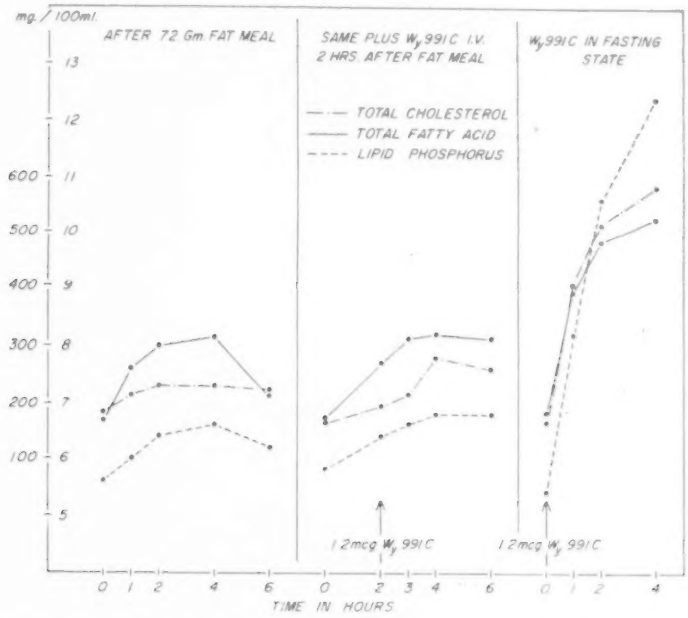

Fig. 5.—Plasma lipid values of A.M., 45 kg. white female with cerebral vascular accident. Some increase in total fatty acid and lipid phosphorus values followed a 72 gm. fat (cream) meal (left panel). Injection of crystalline LM (Wy 991 C) elicited a marked hyperlipemic response during fasting (right panel), but this effect was blocked by prefeeding with the meal of cream (center panel).

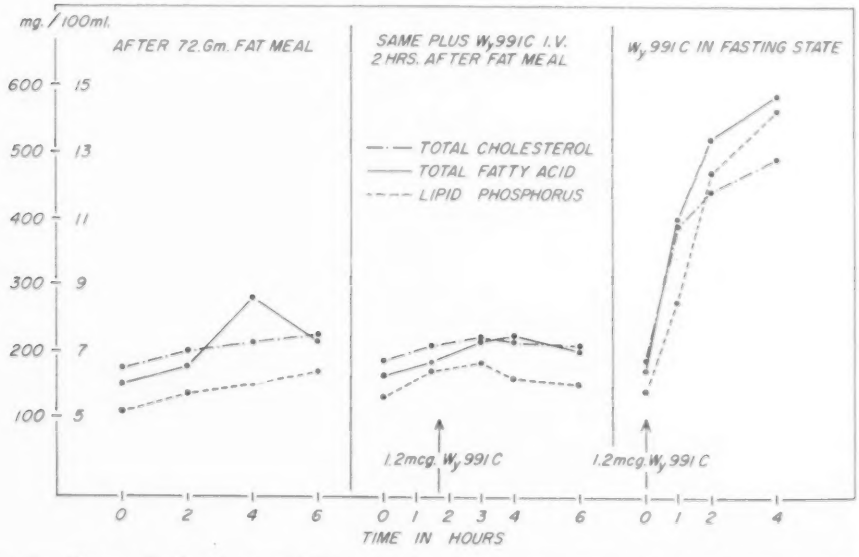

Fig. 6.—Plasma lipid values of J.W., a 50 kg. Negro male with sickle cell anemia, during same sequence of tests with cream feedings and LM as in Fig. 5.

a marked rise in plasma lipids when injected with LM after a 15-hour fast. This was true with both preparations of the hormone, administered in a dosage of 1.2 micrograms of the crystalline material or 5 mg. of the dialyzate per kg. of body weight.

Prefeeding with glucose or amino acids had no effect on the plasma levels of cholesterol, fatty acids, or lipid phosphorus during the study period (Figs. 1 to 4). Following the ingestion of the fat meal, on the other hand, some increase in fatty acids and lipid phosphorus occurred (Figs. 5 to 7). These changes are minimal, however, when compared with those induced by the administration of LM to the same subjects under conditions of fasting.

The effect of prefeeding with glucose, amino acids, or fat on the response to LM is shown in Figs. 1 to 7. It is evident that either glucose or fat ingestion 2 hours prior to the intravenous administration of LM blocked the hyperlipemic effect of this hormone. Under similar conditions, however, an amino acid feeding failed to prevent the LM effects. (Fig. 4, and Table 2).

Discussion. The intravenous administration of lipid mobilizer (LM) elicited an hyperlipemic response in all of these test subjects when they were fasting (Figs. 1 to 7, Table 2). The response was characterized by a sharp two- to threefold increase in plasma cholesterol, fatty acid, and lipid phosphorus values. Prefeeding the subjects with meals of glucose or cream, however, blocked this response, while in the two tests with amino acid meals, no such inhibition occurred. The metabolic basis for these observations is not entirely clear at this time. Never-

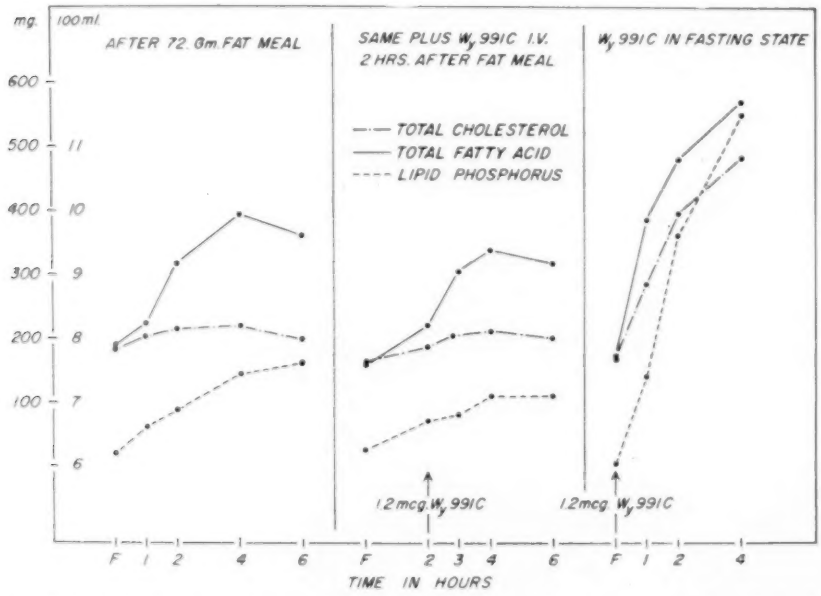

Fig. 7.—Plasma lipid values of G.B., 48 kg. Negro female with chronic granulocytic leukemia, during same sequence of tests with cream feedings and LM as in Figs. 5 and 6. (Compare with Fig. 3 which depicts results of tests with glucose and LM in same subject).

theless, recent experimental studies by Seifter and Baeder[11] would appear to bear directly on certain of these findings These workers had observed that the greatest responsiveness to the hyperlipemic action of LM occurred in animals which had inadvertently been exposed to minute amounts of potential hepatotoxic agents. This led them to study the role of the liver in determining lipid concentrations in the peripheral blood following mobilization of fat from the depots. Sensitization of rats to the effects of LM was achieved by supplementing the regular diet with potassium penicillin G (4 gm. per ton) and 0.005% butylated p-hydroxyanisole. It was found that LM induced an elevation of plasma fatty acids in hepatectomized rats whether fasted or nonfasted, sensitized or nonsensitized, and that the triglyceridemia was not associated with corresponding elevations in cholesterol and lipid phosphorus. Furthermore, livers which contained adequate amounts of glycogen (4%) either retained or metabolized mobilized lipid in sensitized or desensitized rats. On the other hand, livers depleted of glycogen (0.09%) handled the fat load adequately in nonsensitized rats, but not in sensitized ones with resultant hyperlipemia. In these animal studies, the source of excess cholesterol and lipid phosphorus in the LM induced hyperlipemias was the liver.

TABLE 2.—FAILURE OF ORAL PREFEEDING WITH 65 GM. AMINOACIDS TO BLOCK RESPONSE TO LM IN PATIENT H.S.

		Plasma values in mg./100 ml.			
Test	*Time of sample*	*Fatty Acids*	*Total Cholesterol*	*Lipid Phosphorus*	*Aminoacid Nitrogen*
65 gm. aminoacid meal	Baseline*	196	236	5.4	5.6
	1 hr.	184	224	6.0	5.8
	3 hr.	178	228	6.2	6.2
	7 hr.	186	230	6.1	6.1
Same plus 5 mg./kg. LM at end of 2 hrs.	Baseline*	184	212	5.6	5.2
	1 hr.	200	216	6.0	5.0
	2 hr.	224	208	5.8	7.1
	3 hr.	302	296	7.1	6.0
	4 hr.	414	344	8.6	6.2
	5 hr.	438	386	11.2	6.4
	7 hr.	526	408	10.5	6.6
Fasting plus 5 mg./kg. LM	Baseline*	196	185	5.2	5.2
	1 hr.	299	272	8.6	5.6
	2 hr.	352	296	11.4	6.1
	4 hr.	408	358	12.2	6.3

*Baseline specimen drawn just prior to administration of indicated aminoacid meal or LM.

With the above observations in mind, the finding that prefeeding human subjects with glucose inhibited the peripheral hyperlipemic effect of LM is not surprising. Presumably, triglyceride mobilization was induced by LM administration, but was handled by each subject's liver when adequate supplies of glucose were made available to it. This same mechanism also appears to explain the finding of Bragdon, Havel and Gordon[2] that the prefeeding of carbohydrate practically abolished the lipemia producing effect of protamine

in rats. Since the latter phenomenon was shown by Seifter and Baeder[8] to be mediated through the release of LM, the basis of this interpretation is readily apparent. The observations of Levin and Farber[5] that diet, degree of fasting, and pretreatment with glucose had marked influence on lipid mobilization are subject to similar interpretation. It should be clear, furthermore, that the uniform hyperlipemic response to LM administration by all of the subjects tested in this study implies adequate liver glycogen depletion either through prior fasting or by virtue of hepatic derangement by disease or other factors in addition to the period of fasting.

While the observed inhibition of peripheral (antecubital vein) hyperlipemia by prefeeding glucose may be explained by the above indicated mechanism, it does not appear reasonable to assume that prefeeding with cream blocked the LM effect through the same mechanism. In this connection, it may be recalled that daily administration of LM to 2 subjects on a high fat diet failed to develop hyperlipemia, while subjects kept on a very low fat diet readily exhibited hyperlipemia to similar amounts of LM (Zarafonetis *et al.*[14]). It was postulated that in the subjects on a high fat diet a lipid removal or clearing mechanism had been activated, and that this somehow negated the LM potential. Such an interpretation depends, of course, on the existence of an hormonal system for lipid mobilization–lipid deposition, analogous perhaps to the glucagon–insulin mechanism for glucose. Various studies with LM and lipid clearing factors give considerable support to the concept of such a system for the handling of lipids. However, additional clarification, particularly of the clearing factor component, will be necessary before this system is established. In any event, the demonstration of such a system would offer a logical basis for the prevention of LM induced hyperlipemia by prefeeding with fat as observed in this study.

With regard to the failure of amino acid prefeeding to suppress the hyperlipemic effect of LM little can be said at this time. Although some amino acids may be diverted to glucose by the liver, this either did not occur or was performed too slowly to block the LM response in the manner of a glucose meal.

Thus, the acute response to lipid mobilizer hormone may be modified by appropriate dietary measures. Enhancement of the peripheral hyperlipemia is effected by fasting and by substances which sensitize the liver. Prefeeding with glucose does not prevent triglyceride mobilization following LM administration, but it does enable the liver to metabolize the fatty acids in such a manner as to prevent peripheral hyperlipemia. Prefeeding with a meal of cream also prevents post-LM hyperlipemia, but the mechanism for this effect is less clear. Prefeeding with amino acids, on the other hand, did not prevent the peripheral hyperlipemia due to LM injection in the 2 subjects tested. These findings indicate a dissociation of both the influences and the mechanisms by which these influences are mediated for the respective food classes on the acute response to lipid mobilizer hormone.

Aside from the effect of prefeeding on the response to LM, attention should also be drawn to the crystalline LM employed in these studies. The crystalline material was effective in the minute quantity of 0.02 mcg. per kilogram of body weight, which is in keeping with previously reported observations[10]. This compares favorably with the effect produced by 5 mg. per kilogram of the relatively crude plasma dialyzates containing LM in these and

other clinical tests[12,14]. It is characteristic of hormones, of course, that they are effective in minute quantities. The observations with crystalline LM in these subjects, therefore, are consistent with other accumulated data[6-11] which led Seifter and Baeder to designate an hormonal status for this substance.

The importance of the liver on the consequences of lipid mobilization, and the sensitization of the liver with minute amounts of penicillin and an antioxidant, as has been demonstrated by Seifter and Baeder[11], present implications which may be of extreme clinical significance. In this connection, may be mentioned also the findings of Coniglio and Bell[3] and of Anderson and Coniglio[1]. Within 24 hours after feeding aureomycin and streptomycin, neomycin alone, or a mixture of these antibiotics with sulfanilamide, these workers observed increased incorporation of C^{14}-labeled acetate into hepatic fatty acids in all antibiotic treated rats compared to pair-fed controls.

In view of these and other observations, it would seem premature to attribute clinical hypercholesterolemic states to dietary fats primarily. Rather, the problem is highly complex, and many factors must be taken into consideration: genetic determinants; lipid and other dietary constituents; antibiotics, antioxidants, and undoubtedly many other substances which disturb or modify hepatic metabolism; as well as the role of endogenous hormonal derangements, including the lipid mobilizer hormone of Seifter and Baeder. Indeed, studies underway in these laboratories have already shown excess LM activity to be present in the plasma of subjects with familial hypercholesterolemia and hyperlipemia[15]. It is to be hoped that continuation of these investigations will throw additional light on the metabolism of lipids and lead to better understanding of the clinical lipid dyscrasias.

Summary. 1. The consequences of prefeeding with glucose, cream, or amino acids on the hyperlipemic effect of lipid mobilizer hormone (LM) have been studied in man. Meals of glucose or cream, but not of amino acids, were found to block the hyperlipemic response to intravenously administered LM.

2. Evidence is cited which indicates that triglyceride mobilization occurs following LM administration, but that prefeeding with glucose apparently enables the liver to metabolize the lipids presented to it, thereby preventing a peripheral hyperlipemia.

3. It is postulated that inhibition of the hyperlipemic effect of LM by prefeeding with cream is probably mediated through a different mechanism than that ascribed to the glucose meals.

4. As little as 1.2 micrograms of the crystalline LM injected intravenously into fasting subjects elicited a prompt two- to threefold rise in plasma fatty acids, cholesterol, and lipid phosphorus.

5. Attention is drawn to some implications which these and other observations with LM may hold for certain clinical hyperlipemic states.

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SUMMARIO IN INTERLINGUA

Effecto De Pre-Alimentation Super Le Responsa Acute A Hormon Lipido-Mobilisante In Humanos

1. Esseva studiate le consequentias de pre-alimentation con glucosa, crema, o amino-acidos que resulta in humanos in le effecto hyperlipemic de hormon lipido-mobilisante (LM). Esseva trovate que repastos de glucosa o de crema, sed non de amino-acidos, bloca le responsa a LM de administration intravenose.

2. Es citate indicationes que un mobilisation de triglycerido occurre post le administration de LM sed que le pre-alimentation con glucosa rende le hepate apparentemente capace a metabolisar le lipidos presentate a illo, con le resultato que hyperlipemia peripheric es prevenite.

3. Es postulate que le inhibition del effecto hyperlipemic de LM per pre-alimentation con crema es probabilemente mediate per un mechanismo altere que illo ascribite a repastos de glucosa.

4. Non plus que 1,2 microgrammas de LM crystallin injicite per via intravenose in subjectos in stato jejun esseva necessari pro generar un duple o triple augmento del nivellos plasmatic de acidos grasse, cholesterol, e phosphoro lipidic.

5. Es signalate certe consequentias que iste e altere observationes relative a LM va possibilemente haber pro certe statos hyperlipemic clinic.

A NEW LABORATORY METHOD FOR SCREENING DEBRIDING AGENTS

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Many types of preparations have been proposed for the debridement of burns and other types of lesions. Recent studies have been concerned largely with the use of hydrolytic enzymes, particularly the proteases. Most of these agents either failed to remove the necrotic tissue or were irritating to the adjacent living tissues. Progress in this field has been hampered by the lack of suitable laboratory methods for screening and evaluating various lytic agents. This paper is concerned with the development of laboratory methods for these purposes.

Problems involved. In a laboratory test, there is needed a standard substrate which approximates necrotic tissue. In such a tissue are found living and devitalized cells and denatured proteins including collagen, elastin, keratin plus mucopolysaccharides, and lipids. Development of an ideal substrate for use in assay is not only difficult, but the vital relationship between host and debriding agent is left unevaluated in any *in vitro* assay. In view of these shortcomings, it appears most desirable to select an approximate substrate for use in a preliminary, but rapid and reliable, *in vitro* test and to follow this with a detailed study of *in vivo* activity of the enzyme preparation. Thus one can rapidly screen a number of materials and then extensively test the ones showing greatest promise.

1. *In Vitro* Studies. Although there are available many standard proteolytic assays based upon gelatin viscosity reduction, rate of milk clotting, rate of digestion of azo-coll, hemoglobin, casein and others (Anson[1], Kunitz[3], Nickerson[4], Oakley, Warrack and Van Heyningen[5], and Wilstätter *et al.*[7]), none of these *in vitro* analytical tests are conducted under conditions sufficiently comparable to clinical conditions. Results obtained by these methods are a poor guide in predicting clinical performance; one procedure, however, has been found to be an approximate index of *in vivo* action. This method, referred to as spun collagen-fiber assay, consists of measuring the time required for a preparation to break a collagen thread to which a small weight is attached. The substrate employed is fairly representative of the largest component of skin, and can readily be prepared in reproducible quantity. The state of denaturation of this form of collagen lies somewhere between native collagen and hide powder.

2. *In Vivo Studies.* The diversity of lesions requiring debridement in the human cannot be simulated by a simple wound in a laboratory animal. In man, the lesions are produced by a multi-

plicity of causes and there results a great variation in the extent of damage and the composition of the necrotic material. Burns, for example, may be classified according to the primary cause of injury (chemical or thermal) as well as the severity of injury (first degree, second degree, or third degree). Great differences are also encountered in burns inflicted by different agents, for example, hot water compared to a flash burn produced by an acetylene torch. Ulcers also are variable lesions with an abundance of fibrinous and purulent accumulations. For preclinical investigations, therefore, an effective *in vivo* assay employing the most refractory lesion is essential in evaluating the many preparations which successfully pass the digestion criteria of the *in vitro* tests. Despite the difficulties and limitations associated with the use of a standard wound in animals, an objective procedure has been developed which has proved useful and reliable in predicting clinical performance of debriding preparations.

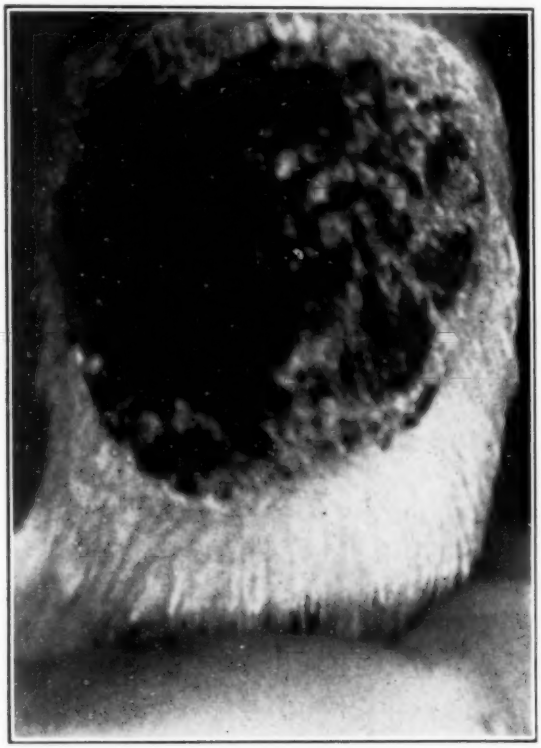

Fig 1.—Seven-day-old guinea pig scald eschar.

Methods. 1. *In Vitro.* The spun collagen-fiber assay consists of suspending a loaded forty-filament collagen thread (113 mg./meter) in the preparation under test and determining the time required for the fiber to break. The collagen obtained by the method of Salo and Waugh[6] supports a 2 gm. weight at 37° C. The time necessary for breaking of the fiber by the protease is automatically recorded. Essentially the method is a refinement of that described by

Kraissl[2] for determination of *in vitro* catgut digestion.

2. *In Vivo.* Each guinea pig (male) is anesthetized by intraperitoneal administration of pentobarbital sodium and the dorsal hair closely cut with an electric clipper. The back of the animal is then immersed in a water bath at 70° C. for 45 seconds to produce a third degree burn covering approximately 20% of the body surface (5 cm. in diameter).

These conditions were selected for convenience; higher temperatures are harder to maintain in a water bath and lower temperatures require a longer burning time. Upon subjection to heat, the area becomes pink, followed by edema and a slow blanching until it is an ash white. The eschar which then forms gradually is greatly accelerated if several animals are kept in one cage. Apparently the activity of the pigs helps remove the thin keratin layer enabling earlier development of the eschar. After one week a thick hard leathery eschar has formed (Fig. 1) and is then treated with the debriding agent in a water soluble jelly base. The wound is dressed with a vaseline impregnated gauze or plain gauze interlayed with a plastic film and held in place with adhesive tape. Daily applications of enzyme preparation are made for 3 days with estimation of tissue digestion being made at each dressing change. Experiments are carried out in triplicate. Mortality of the animals due to the rigorous conditions of circumferential taping is between 10 and 20% at the end of the entire experimental period or less than 5% after 2 treatments.

Results and Discussion. The results of the *in vitro* test do not correlate directly with the results of the animal studies but the test serves as a screening tool. Thus a preparation must break the forty-filament strand in less than 35 minutes to be considered for *in vivo* study. Preferably it should have a collagen digestion time of less than 30 minutes. This is illustrated in Table 1.

The *in vivo* assay was found to be quite reproducible particularly after 3 days of treatment. Table 2 illustrates the type of response obtained when one enzyme was employed in a number of tests. Similar duplications of test findings were obtained when other proteases were tested under the same experimental conditions. Because of our interest in DEBRICIN* *Ficus* Protease we have studied that material intensively. Figures 2, 3, and 4, illustrate the effect of this protease on a 7-day-old guinea pig scald eschar after periods of 24, 48, and 72 hours. These 2 procedures, therefore, provide an effective means for evaluating potential debriding agents, particularly protease formulations. One can screen rapidly materials utilizing the spun collagen fiber technique and then select the promising preparations for more quantitative determinations of activity with reference to debridement employing the guinea pig eschar technique. It might be noted that *in vitro* use of guinea pig eschar was found to be an unreliable test procedure.

TABLE 1.—COMPARATIVE RESULTS *IN VIVO* AND *IN VITRO* ASSAY PROCEDURES

Material Tested	*pH*	*In Vitro* Spun Collagen Breaking Time*	*In Vivo† % Eschar Debrided After 3 Days of Treatment*
DEBRICIN Ficus Protease	5.0	27 minutes	95
Trypsin	7.0	42 minutes	0
Papain	5.0	61 minutes	Sl. Action

*0.2% solution of enzyme in 0.1M buffer. The shorter the time the greater the enzyme's activity.

†7.5% enzyme in buffered water-soluble base. A 7-day-old guinea pig burn eschar.

Summary. A method is described for laboratory evaluation of debriding preparations utilizing a standard guinea pig burn as *in vivo* test material and spun collagen fiber assay for *in vitro* studies.

*Johnson & Johnson purified protease derived from *Fiscus* latex.

TABLE 2.—*IN VIVO* DEBRIDING ACTIVITY OF DEBRICIN FICUS PROTEASE PREPARATION ON 7-DAY-OLD GUINEA PIG SCALD ESCHARS

Enzyme Tested	*Experiment Number*	*% of Eschar Debrided After*		
		1 day	*2 days*	*3 days*
DEBRICIN Ficus Protease	105	20	98	100
	105	30	100	100
	105	Action	50	100
	105	0	10	80
	105	0	95	100
	105	15	88	100
	99	0	30	98
	99	0	30	98
	99		25	80
	98	Sl. Act.	70	Dead
	98	Sl. Act.	75	98
	98	Sl. Act.	70	95
	95	0	10	Dead
	95	0	No. Act.	95
	95	0	25	100
	95	0	90	Dead
	95	0	98	100
	95	0	85	100
	95	0	65	100
	95	0	20	100
	82	0	75	100
	82	0	75	100
	82	0	80	100
	82	0	85	100
	82	0	80	Dead
Control Jelly Base	95	0	0	0
	95	0	0	0

Fig. 2.—Seven-day-old guinea pig scald burn treated for 24 hours with DEBRICIN enzyme (one application).

Fig. 3.—Seven-day-old guinea pig scald burn treated for 48 hours with DEBRICIN enzyme (two applications).

Fig. 4.—Seven-day-old guinea pig scald burn treated for 72 hours with DEBRICIN enzyme (three applications).

The animal assay consists of treating a 7-day-old scald eschar on a guinea pig with the preparation under test. The eschar is produced by partial immersion of the animal in water at 70° C. for 45 seconds. Daily applications of the preparation are made for 3 days and the degree of debridement determined at each dressing change.

The *in vitro* technique measures the time required to break a 40 filament collagen strand at 37° C. The fiber under standard tension is suspended in the preparation being investigated.

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SUMMARIO IN INTERLINGUA

Un Nove Methodo Laboratorial Pro Le Evalutation De Agentes De Debridement

Es describite un methodo pro le evalutation laboratorial de preparatos debridante. Illo utilisa un arditura standard in porcos de India como base experimental in tests *in vivo* e le essayo del lyse de filate fibras collagenic in tests *in vitro*.

In le experimento animal, le preparato a testar es usate pro tractar un eschara formate in un porco de India in consequentia de un escaldatura que esseva effectuate 7 dies previemente per le immersion partial del animal durante 45 secundas in aqua de 70 C de temperatura. Le application del preparato es repetite diurnemente durante un periodo de 3 dies, e omne vice le grado de debridement effectuate es determinate.

Le technica usate *in vitro* mesura le tempore requirite pro rumper un cordon de 40 filamentos de collageno a 37 C de temperatura. Le cordon es suspendite sub un tension standard in le preparato a testar.

COMPARATIVE LABORATORY STUDY OF THE DEBRIDING EFFECT OF SIX ENZYMES

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Enzyme treatment of wounds containing accumulations of necrotic tissue has been practiced widely as an adjunct to therapy. A search for new agents has progressed at a slow pace. The delay has been attributed largely to the lack of an *in vivo* screening method to bridge the gap between *in vitro* studies and clinical trials. Recently an *in vivo* method for screening debriding agents was presented[1]. We have examined a new protease by this method and have compared the activity of this preparation and five well-known commercial enzyme and proprietary preparations.

Experimental. The general techniques employed were as described previously[1]. Seven-day-old guinea pig scald eschars were used as the *in vivo* substrate. The eschars were dressed daily for 3 days. The ethical preparations were used under the conditions prescribed by the manufacturers, while other enzymes were used in a water-soluble jelly base, as outlined in Table 1.

TABLE 1.—ENZYME PREPARATIONS

Enzyme	*Source*	*Concentration*	*pH*
1:250 Bacto-trypsin	Difco	7.5%	7.5
Crystalline trypsin	TRYPTAR–Armour	1.0%	7.0
Streptokinase-streptodornase	VARIDASE–Lederle	100,000 u SK 25,000 u SD per 15 ml. jelly	7.5
Papain	Optimo–Penick	7.5%	5.0
Papain-chlorophyll-urea	PANAFIL–Rystan	10.0%	6.4
Purified fig latex protease	DEBRICIN–Johnson & Johnson	7.5%	5.0
Jelly Base Controls			5.0 7.0

Fig. 1.—Seven-day-old guinea pig scald burn treated for 72 hours with TRYPSIN (three applications).

Fig. 2.—Seven-day-old guinea pig scald burn treated for 72 hours with CRYSTALLINE TRYPSIN (three applications).

Fig. 3.—Seven-day-old guinea pig scald burn treated for 72 hours with PAPAIN (three applications).

Fig. 4.—Seven-day-old guinea pig scald burn treated for 72 hours with PAPAIN-CHLOROPHYLL-UREA (three applications).

Fig. 5.—Seven-day-old guinea pig scald burn treated for 72 hours with STREPTOKINASE-STREPTODORNASE (three applications).

Results and Discussion. The observations are tabulated in Table 2. Fig latex enzyme was found to exhibit strong debriding activity, while the other preparations failed to achieve more than a softening of the eschar. Figures 1 through 5 and Fig. 4 in the preceding article illustrate the action of the various preparations after 72 hours of treatment (3 applications). Figures 2 and 3 of the preceding article show the effect of the fig latex protease after 24 and 48 hours.

Summary. Six enzyme preparations were examined for debriding activity on full-thickness animal burns. The enzymes examined included trypsin, crystalline trypsin, papain, papain-chlorophyll-urea, streptokinase-streptodornase, purified fig latex protease, and jelly base controls (pH 5.0 and pH 7.0). Fig latex protease was found to exhibit strong debriding activity, while the other preparations failed to achieve more than a softening of the eschar.

TABLE 2.—*IN VIVO* DEBRIDING ACTIVITY OF VARIOUS ENZYME PREPARATIONS ON 7-DAY-OLD GUINEA PIG SCALD ESCHARS

	*Average % of Eschar Debrided After**		
Enzyme	*1 Day*	*2 Days*	*3 Days*
Trypsin	0	0	0
Crystalline Trypsin	0	0	0
Papain	0	5	5
Papain-chlorophyll-urea	0	0	0
Streptokinase-streptodornase	0	0	0
Purified fig latex protease	5	65	95
Jelly Base Controls (pH 5.0)	0	0	0
(pH 7.0)	0	0	0

*Four guinea pigs were used per enzyme, and the eschars were dressed daily for 3 days.

dornase, and a purified fig latex protease. A new protease derived from fig latex was most active in solubilizing the necrotic tissue.

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SUMMARIO IN INTERLINGUA

Comparative Studios Laboratorial Del Effectos Debridante De Sex Enzymas

Sex preparatos enzymatic esseva examinate pro lor activitate debridante in escaldaturas del tertie grado in porcos de India. Le enzymas examinate esseva trypsina, trypsina crystallin, papaina, papaina-chlorophylla-urea, streptokinase, streptodornase, e un nove protease derivate ab purificate latex de fico. Iste ultime esseva le plus active como solvente de histos necrotic.

SUMMARIO IN INTERLINGUA

(See page 387 for original article)

Syndrome De Cushing, Producite Per Le Administration De Normal Doses De Reimplaciamento De Cortisona In Un Patiente Con Defecto Del Mechanismo De Degradation Steroide

Es presentate le caso de un patiente in qui panhypopituitarismo occurreva post un operation pituitari pro acromegalia. Sub le tractamento de reimplaciamento con androgeno e 25 mg de cortisona per die in administrationes oral, le patiente disveloppava multes del manifestationes de hyperadrenocorticismo (syndrome de Cushing). Le uso de un therapia thyroide non habeva essite considerate a causa del absentia de signos de hypothyroidismo, ben que le acceptation de radio-iodo e le nivello de iodo ligate a proteina monstrava valores de magnitude hypothyroide. Tests del function hepatic esseva etiam anormal. Le globulina seral esseva elevate; le test de flocculation a cephalina e le test de turbiditate a thymol esseva positive; retention de Bromsulfaleina esseva presente.

Con reimplaciamento thyroide (2 granos USP per die) e mantenentia del dosage de androgeno e cortisona, omne le manifestationes de hyperadrenocorticismo dispareva ante que le tests del function hepatic retornava al norma. Nulle causa pro le anormalitate del tests hepatic esseva apparente.

Le rapiditate del disparition de injectiones de hydrocortisona esseva studiate in iste patiente. Le valores obtenite ante le tractamento con thyroide correspondeva al valores previemente reportate in le caso de patientes con myxedema e con cirrhosis hepatic. Mesmo quando omne indicios de hyperadrenocorticismo habeva disparite, le disparition de hydrocortisona in iste patiente non attingeva un rapiditate normal.

Le autores exprime le opinion que in evalutar syndromes que es causate per quantitates excessive de un hormon normal, le factores que concerne le metabolismo de ille hormon debe esser considerate seriemente. In casos in que le mechanismos pro le elimination del hormon es obstruite, quantitates normal del hormon pote devenir quantitates que es physiologicamente excessive.

STUDIES OF HEPATIC FUNCTION IN PATIENTS RECEIVING PROMAZINE*

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Promazine is a phenothiazine derivative which has been shown to be effective in the management of patients with mental and emotional disturbances (Azima and Durost[1], Fazekas *et al.*[6], and Hollister[10]). This effect is apparently similar to that of chlorpromazine which has been widely used in the treatment of many mental disorders. The numerous reports (Kelsey *et al.*[12], Lemire and Mitchell[15], Loftus *et al.*[16], and Werther and Korelitz[30]) of the occurrence of jaundice in chlorpromazine-treated patients has led to the acceptance (Hollister[9], and Shay and Siplet[24]) of a small but definite incidence of jaundice as a toxic effect of this drug. The mechanism of the production of the jaundice has not been elucidated, but clinical and histologic studies have been considered consistent with an intrahepatic cholestasis (Stein and Wright[26]).

Promazine differs from chlorpromazine only in the absence of the chlorine atom from the carbon 2 position of the phenothiazine nucleus. Only one patient has been reported (Kemp[13]), thus far, to have developed jaundice during the administration of promazine. This patient had also received chlorpromazine prior to being given promazine. In the present study a large number of patients receiving promazine were carefully observed for the development of jaundice.

In one-half of this group, the effect of the drug on the liver was studied by serial determinations of hepatic function. No evidence of jaundice or hepatic damage developed in patients receiving this drug.

Methods. During the period of this study 201 patients have received promazine§. One-hundred and ten of these have had a battery of liver function studies performed. These studies included the Bromsulphalein excretion test, the thymol turbidity and cephalin flocculation tests, alkaline phosphatase and bilirubin levels and determination of the serum proteins. In 35 patients serum glutamic oxaloacetic transaminase and lactic dehydrogenase determinations also were performed.

*Supported in part by a grant from Wyeth Laboratories, Radnor, Pennsylvania.

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§The promazine (Sparine) was provided through the courtesy of Wyeth Laboratories, Radnor, Pennsylvania.

(In a few patients glutamic pyruvic transaminase levels were determined.) The methods employed and the normal values are shown in Table 1. Hepatic function was determined before the initiation of promazine therapy and at the intervals thereafter shown in Table 2. In the remaining 91 patients, evaluation consisted of clinical observation or incomplete studies of hepatic function. The doses of promazine used and the duration of therapy are shown in Fig. 1.

TABLE 1.—LIVER FUNCTION TESTS PERFORMED IN 110 PATIENTS ON PROMAZINE THERAPY

	Method:	*Normal Value:*
Bilirubin	Malloy and Evelyn modification of the van den Bergh reaction[18].	1.0 or less
Bromsulphalein excretion	Modification of Mateer[19] (5 mg./kg. and 45 min. specimen).	5 or less
Thymol turbidity	Maclagen, modified by Shank and Hoagland[17,23].	4 or less
Cephalin flocculation	Modification of Hanger and Neefe and Reinhold[8,21].	2+ or less
Alkaline phosphatase	Bodansky[2].	4.5 or less
Total Proteins:	Weichselbaum modification of Kingsley biuret method[14,20].	
Albumin		3.8 or more
Globulin		3.0 or less
Serum protein analysis	Paper strip electrophoresis[4].	
Glutamic oxaloacetic transaminase	Initially Karmen; later Reitman and Frankel modification of the colorimetric method of Umbreit[11,22].	Less than 40 units
Glutamic pyruvic transaminase		Less than 40 units
Lactic dehydrogenase	Zimmerman and Weinstein[32].	Less than 270 units

TABLE 2.—INTERVAL BETWEEN INITIATION OF THERAPY AND LIVER FUNCTION STUDIES

Interval in Weeks	*No. of Patients*
1	23
2	18
3	19
4	13
5	4
6–8	17
9–20	17
20–36	11

Results. One-hundred and ten patients receiving promazine were studied with liver function tests, as described above. Seventy-seven of this group had normal results or showed improvement of abnormal values while receiving promazine (Table 3). The 44 patients, whose liver function remained normal throughout the period of study, received promazine for periods as long as 10½ months with the total dose as high as 56,400 mg. (Fig. 1). In 33 patients with initially abnormal hepatic function (Table 3) there was progressive improvement, commensurate with their clinical diagnosis of cirrhosis or fatty metamorphosis of the liver, during the period of promazine administration. Five patients with initially abnormal hepatic function (Table 3) showed no change in the degree of abnormality during therapy.

Twenty-eight of the patients studied had hepatic dysfunction which was associated with their primary disease. The effects of promazine on these patients cannot be well evaluated, but

TABLE 3.—EFFECT OF PROMAZINE ON LIVER FUNCTION

Initial Results	*No. of Pts.*	*No Change*	*Improved*	*Worsened*
Normal	44	44	0	0
Abnormal	38*	5	33	0

*This number does not include the 28 patients with hepatic dysfunction associated with their primary disease that could not be evaluated (see text).

function and all subsequently expired.

Alcoholic fatty cirrhosis was present in 10 of these patients. Two with bleeding esophageal varices and slight jaundice died in hepatic coma. One patient with deep jaundice on entry died suddenly on the third hospital day. The other 7 patients entered and were treated for delirium tremens before

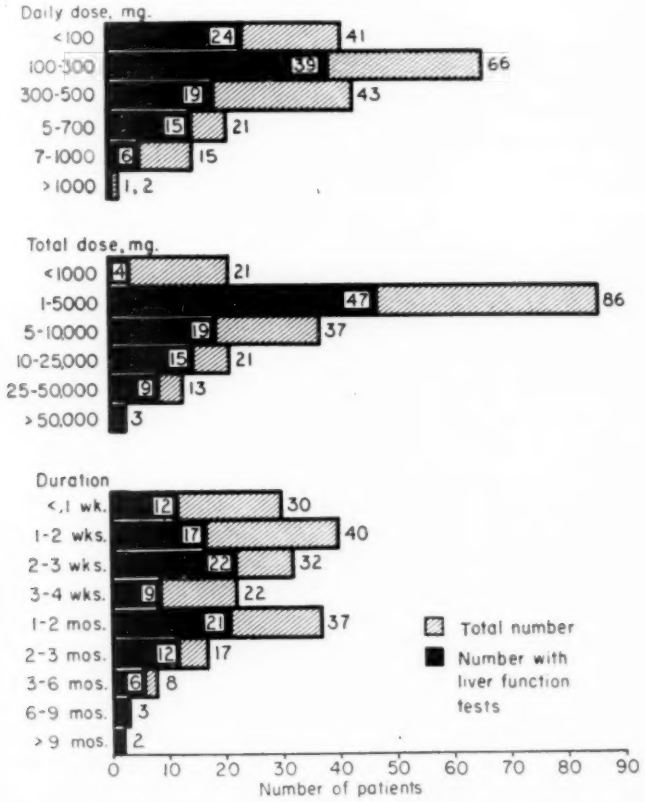

Fig. 1.—Daily and total doses of promazine and the duration of promazine therapy.

in all their clinical course was considered consistent with their basic disease.

Eight of the 28 had metastatic carcinoma, 2 had advanced Hodgkin's disease and 1 patient had severe systemic lupus erythematosus. All these patients had abnormalities of liver

liver function tests could be obtained. Subsequent liver function tests yielded abnormal results consistent with the severity of the hepatic disease. None of these patients developed clinical jaundice.

Severe congestive heart failure was

present in 7 patients. In these patients promazine was administered prior to the performance of liver function tests. In all 7 patients hepatic function abnormality consistent with the severity of the heart failure was observed. Two of these patients had varying hepatic dysfunction associated with fluctuations of intractable heart failure. In one patient impaired Bromsulphalein excretion remained unchanged throughout the period of study. Four patients died of their heart disease after only 1 set of function tests.

The hepatic dysfunction in this group of patients was considered characteristic of metastatic carcinoma (Thomas and Zimmerman[27]), alcoholic fatty cirrhosis (Zimmerman[31]), and congestive heart failure (Evans *et al.*[5]). A possible effect of promazine obscured by the primary disease cannot be excluded.

The additional 91 patients who received promazine had incomplete or no liver function studies; jaundice was not observed in any of these.

Discussion. In 82 patients studied by a battery of tests, the administration of promazine resulted in no impairment of liver function. Even in the 38 patients with initially abnormal function there was no worsening, and in 33 of these there was improvement as the primary disease improved during the administration of the drug. The high incidence of initial hepatic dysfunction was related to the fact that promazine was frequently used for the treatment of alcoholic patients with delirium tremens. As has been indicated above, jaundice did not develop in any of the 201 patients who were treated with promazine. The drug was administered for periods up to 10½ months and in daily doses as high as 1400 mg.

From this study of only 200 patients who did not develop jaundice while receiving promazine, no estimate of the incidence of jaundice in promazine-treated patients can be made. It is apparently lower than the 1 to 5% incidence reported (Shay and Siplet[24]) for chlorpromazine. This impression is supported by the rarity of reports of jaundice attributable to promazine administration, although the drug has been given to more than 4 million patients*. Furthermore, the lack of development of hepatic dysfunction in patients receiving promazine, observed in the present study, contrasts with the 20% incidence of hepatic functional abnormality in 47 patients receiving chlorpromazine, reported by Shay and Siplet[24]. Dickes, Schenker and Deutsch[3] have also described a high incidence of hepatic dysfunction in 50 patients receiving chlorpromazine. Azima and Durost[1] have also reported a 25% incidence of elevation of serum alkaline phosphatase in patients receiving chlorpromazine. These authors observed only a 4% incidence of development of this abnormality in patients receiving promazine.

Two additional patients, who have developed hepatic dysfunction while receiving promazine, have been reported. Both had received chlorpromazine also. One of these reported by Waitzkin[28] had had a recurrence of jaundice after the re-administration of chlorpromazine. Two months later he was given promazine for 6 days and developed nausea, vomiting and urticaria with recurrence of Bromsulphalein retention but without clinical jaundice or significant elevation of alkaline phosphatase. The other patient was reported (Kemp[13]) to develop clinical jaundice 2 days after promazine administration. He had also received chlorpromazine for a 2-week period ending 18 days before the onset of jaundice. In this case the author postu-

*This figure was provided by Wyeth Laboratories.

lated that the patient had been "sensitized" by the chlorpromazine and had developed jaundice with promazine administration because of the similarity of the chemical structure of the two drugs.

There have been 12 patients reported, who have received promazine after episodes of chlorpromazine jaundice without recurrence of jaundice or hepatic dysfunction (Hollister[10], Shay[25], and Waitzkin[28]). In the 3 patients studied by Shay[25] and in 5 of the patients studied by Hollister[10], readministration of chlorpromazine again resulted in jaundice or hepatic dysfunction.

The mechanism by which chlorpromazine produces jaundice is not well understood at this time. The absence of jaundice with the administration of an almost identical drug (promazine) raises an interesting pharmacologic question. The only structural difference between the two drugs is the presence of the chlorine atom in chlorpromazine. While halogenation, and particularly chlorination, of some hydrocarbons confers hepatotoxic properties on the molecule, this does not appear to be the mechanism of chlorpromazine-induced jaundice or hepatic dysfunction. There is no definite evidence that patients with hepatic disease are made worse by chlorpromazine. The few reports of disappearance of jaundice with continued administration of chlorpromazine is inconsistent with hepatotoxicity as the basis of chlorpromazine jaundice. Hollister[10], Shay[25] and many others have suggested that chlorpromazine-jaundice is the result of drug allergy or "sensitization." Gutman[7] in a recent editorial has discussed this problem and concluded that the intrahepatic cholestasis resulting from chlorpromazine and other drugs is a manifestation of drug hypersensitivity, although the precise mechanism is obscure.

Summary and Conclusions. Jaundice did not develop in any of the 201 patients treated with promazine. Hepatic function was evaluated in 82 of these patients before and after promazine. Hepatic function remained normal in 44 and improved in 33 of the 38 previously abnormal. In no patients receiving promazine was there worsening of function.

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SUMMARIO IN INTERLINGUA

Studios Del Function Hepatic In Patientes Qui Recipe Promazina

Nulle jalnessa se disveloppava in 201 patientes tractate con promazinea. In 82 del casos, evalutationes del function hepatic esseva effectuate ante e post le curso de promazina. In 44 casos le function hepatic esseva normal ante e post le therapia. In 38 casos le function hepatic esseva anormal ante le therapia. In 35 de istos, le function hepatic esseva meliorate post le therapia. Pejoration del function hepatic resultava in nulle del patientes tractate con promazina.

A MODIFICATION OF THE THROMBOPLASTIN GENERATION TEST

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The thromboplastin generation test of Biggs and Douglas[3] has been a valuable means of studying defective thromboplastin formation. In the test, platelets, absorbed plasma and serum are mixed together. Calcium is added and the mixture is incubated at 37° C. Samples are taken at regular intervals and the thromboplastin activity is tested on a substrate of platelet-poor plasma. By this procedure patients lacking Christmas (P.T.C.) factor may be distinguished from those lacking antihemophilic factor. Recently it has been reported that Christmas (P.T.C.) activity is increased above normal levels in certain individuals following a meal with a high content of animal fat (Mustard[5]).

One objection to the test is the use of serum as a source of Christmas (P.T.C.) factor. There is evidence that Christmas (P.T.C.) factor takes part in a preliminary reaction to form an active intermediate product (Bersagel and Hougie[2]). Hence the addition of serum in the ordinary way of doing the test might fail to detect important abnormalities in the earlier stages of thromboplastin formation. In this study the test was modified by substituting dilute plasma for serum.

Procedure. Blood was drawn by clean venipuncture into a silicone coated syringe, 9 ml. of the blood was mixed with 1 ml. of 3.8% sodium citrate solution in a 15 ml. silicone-coated centrifuge tube. After spinning at 3000 r.p.m. for 10 minutes the plasma was removed. The following incubation mixture was prepared: 0.5 ml. of Imidazole buffer pH 7.2; 0.3 ml. platelet substitute* (Bell and Alton[1]); 0.3 ml. normal alumina plasma diluted 1 in 5 with physiologic saline; 0.1 ml. of normal or test plasma diluted 1 in 20 with physiologic saline; and 0.3 ml. of M/40 calcium chloride solution.

The mixture was placed in a water bath at 37° C. and at 2-minute intervals 0.1 ml. samples were added to 0.1 ml. aliquots of platelet-poor normal plasma and M/40 calcium chloride solution.

Results. When plasma from different patients was tested and compared with normal plasma the clotting time of the substrate was either normal, increased or shortened.

NORMAL OR DECREASED CLOTTING ACTIVITY IN THE INCUBATION MIXTURE. Table 1 shows the results when the substitution of dilute plasma for serum resulted in normal or delayed clotting of the substrate. The Dicumarol plasma was from a patient who, after 3 weeks on Dicumarol, had a one-stage prothrombin time of 26 seconds (normal 15 seconds). The patient with a deficiency of prothrombin had secondary carcinoma involving the liver and a one-stage prothrombin time of 43 seconds. When normal serum was added

*The platelet substitute was diluted 1/100 with physiologic saline. If the shortest time of clotting of substrate was less than 20 seconds the platelet substitute was diluted further to bring the clotting time into the range 20 to 30 seconds.

to this plasma the prothrombin time of the mixture was not corrected. The factor VII deficient plasma was from a patient with congenital factor VII deficiency and a prothrombin time of 26 seconds completely corrected by normal serum. The Christmas (P.T.C.) deficient plasma was obtained from a member of a family suffering from Christmas disease (MacMillan, Ezrin and Butler[4]).

TABLE 1.—CLOTTING TIME OF SUBSTRATE IN SECONDS WHEN DILUTE PLASMA SHOWED NORMAL OR REDUCED ACTIVITY

Mixture of buffer, platelet substitute alumina plasma with	*Incubation for minutes*				
	2	*4*	*6*	*8*	*10*
Serum	52	11	10	10	12
Normal plasma	73	31	23	22	22
Dicumarol plasma	94	49	30	29	30
Prothrombin deficient plasma	103	37	26	24	23
Factor VII deficient plasma	70	28	23	22	22
P.T.C. Christmas Plasma	75	44	38	37	35

INCREASED CLOTTING ACTIVITY IN THE INCUBATION MIXTURE. Plasma from certain individuals caused the substrate to clot more quickly than normal. Given below are brief case histories and the results are shown in Table 2.

Case Reports. CASE 1. A woman with cyclic thrombocytopenia had plasma which consistently shortened the clotting time. The platelets fell regularly from a normal level to less than 10,000 per cubic ml. with attacks of purpura occurring approximately every 4 weeks.

CASE 2. A 42-year-old man with Buerger's disease developed sudden occlusion of the right femoral artery following lumbar sympathectomy.

CASE 3. A 50-year-old man had thrombosis of the aortic bifurcation. The plasma was consistently lipemic but cleared with spaced-fat feeding. With the disappearance of lipemia the activity of the plasma returned to normal.

CASE 4. A 65-year-old man with carcinoma of the prostate gland showed powerful fibrinolytic activity of the plasma. The one-stage prothrombin time was 26 seconds and plasma fibrinogen was 100 mg. per 100 ml.

CASE 5. A 67-year-old man received treatment at home with Dicumarol following myocardial and pulmonary infarction. Bleeding occurred when the prothrombin time was 55 seconds. Despite 120 mg. of vitamin K_1 in divided doses he bled from the bowel for one week. The prothrombin time slowly returned to normal. The plasma activity then became increased above normal and 10 days after the last sign of bleeding he suffered a pulmonary infarct followed by signs of venous thrombosis in the leg.

TABLE 2.—CLOTTING TIME OF SUBSTRATE IN SECONDS WHEN DILUTE PLASMA SHOWED INCREASED ACTIVITY

Mixture of buffer, platelet substitute alumina plasma with	*Incubation for minutes*				
	2	*4*	*6*	*8*	*10*
Serum	63	12	10	10	11
Normal plasma	73	36	30	30	32
Thrombocytopenic plasma	26	23	25	25	25
Buerger's disease plasma	50	15	15	16	18
Hyperlipemic plasma	30	22	22	24	—
Fibrinolytic plasma	20	14	12	11	12
Post Vitamin K_1 plasma	42	17	15	14	14

The activity of normal plasma was studied following storage and upon dilution with plasma from a patient lacking Christmas (P.T.C.) factor. Plasma with reduced activity was mixed with normal plasma and plasma with increased activity. The activity of the mixture was then determined.

EFFECT OF STORAGE ON NORMAL PLASMA. The activity of normal plasma increased progressively when stored at minus 20° C. This could be prevented if the plasma was spun rapidly at 15,000 r.p.m. for 5 minutes to remove platelets before storage.

CORRECTION OF REDUCED PLASMA ACTIVITY BY MIXING WITH NORMAL PLASMA

AND PLASMA SHOWING INCREASED ACTIVITY. Plasma with reduced activity was mixed in equal parts with normal plasma and plasma having increased activity (Table 3). The mixtures that contained Christmas (P.T.C.) plasma were corrected better by both normal plasma and plasma with increased activity than were the mixtures that contained Dicumarol plasma.

DILUTION CURVE OF NORMAL PLASMA. Serial dilutions of normal plasma were prepared using plasma from a patient with Christmas disease as diluent. The clotting time of the dilute normal plasma was progressively prolonged as the dilution increased (Table 5). A straight line relationship was noted when results were plotted on double logarithmic paper (Fig. 1).

PLASMA ACTIVITY AND PROTHROMBIN TIME. The plasma from patients on Dicumarol showed a decrease in activity that was often similar in the degree to the change in the prothrombin time. An important exception was the patient who developed severe bruising when the prothrombin time was only 22 seconds (normal 15 seconds). The modified thromboplastin generation test showed a marked decrease in activity and gave results similar to those obtained on a patient taking Dicumarol whose prothrombin time was 36 seconds (Table 4).

TABLE 3.—MIXTURES WERE PREPARED OF DICUMAROL AND CHRISTMAS PLASMA WITH PLASMA POSSESSING NORMAL AND INCREASED ACTIVITY (CYCLIC THROMBOCYTOPENIC PLASMA). CLOTTING TIME OF SUBSTRATE RECORDED IN SECONDS

	Minutes of Incubation			
	2	*4*	*6*	*8*
Mixture 1—N + Dicumarol	50	32	28	25
2—N + Christmas	44	25	17	20
3—Cyclic Thrombocytopenic + Dicumarol	56	28	19	17
4—Cyclic Thrombocytopenic + Christmas	39	17	13	13

TABLE 4.—COMPARISON OF ONE-STAGE PROTHROMBIN TIME AND PLASMA ACTIVITY IN 2 PATIENTS RECEIVING DICUMAROL. CLOTTING TIME OF SUBSTRATE RECORDED IN SECONDS

	Incubation for minutes			
Plasma	*2*	*4*	*6*	*8*
Normal	53	33	27	26
Dicumarol patient with bruising prothrombin time 22 seconds	51	43	38	37
Dicumarol patient prothrombin time 36 seconds	65	51	36	38

TABLE 5.—DILUTIONS OF NORMAL PLASMA WERE PREPARED USING PLASMA FROM A PATIENT WITH CHRISTMAS DISEASE AS DILUENT

% of normal plasma	100	50	25	12.5	6
Clotting time of substrate in seconds	27	37	52	68	86

Discussion. In this modification of the thromboplastin generation test, dilute plasma was substituted for serum. Normal plasma contains prothrombin, Christmas (P.T.C.) factor, factors V and VII and antihemophilic factor. At first sight the use of dilute plasma seems to increase the number of variables in the test system and might make the interpretation of results more difficult. Here Factor V and antihemophilic globulin were already supplied by the absorbed plasma and the small amounts of these substances in the dilute plasma would be unlikely to make any significant difference in the yield of thromboplastin. The prothrombin however, could, by

conversion to thrombin, accelerate the formation of thromboplastin. When plasma with reduced content of prothrombin was substituted for normal plasma the time of clotting of the substrate was normal. This suggested that the prothrombin content of the

nation of the level of Christmas factor could be made by referring to the dilution curve of normal plasma. In one such patient undergoing dental extraction this measurement was helpful in regulating the amount of blood transfused.

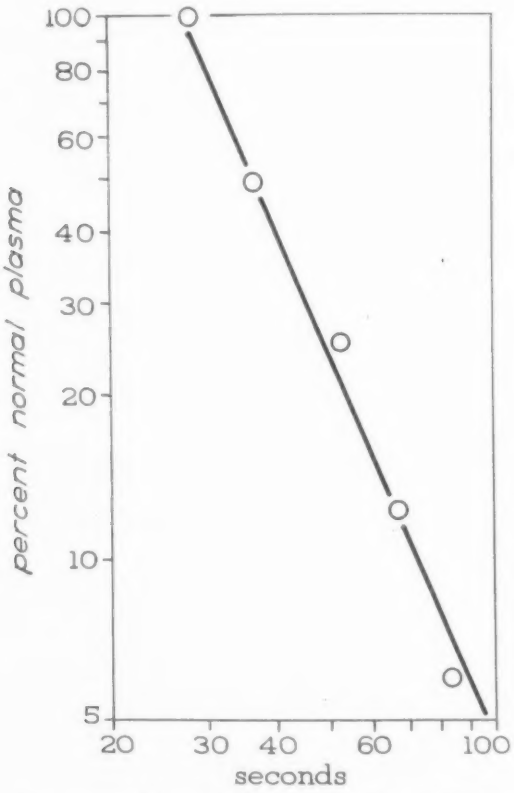

Fig. 1.—Dilution curve prepared from normal plasma using Christmas plasma as diluent.

mixture was not an important variable. Similarly when plasma from a patient with a congenital lack of factor VII was used the substrate again clotted normally. Defective formation of thromboplastin occurred only when plasma from patients receiving Dicumarol or suffering from Christmas disease was substituted in the test. In patients with Christmas disease quantitative determi-

The increased activity of certain plasmas was very interesting. In some patients it approached the activity of normal serum in the test system. Such patients frequently had clinical evidence of thrombosis, for example, the patient with aortic thrombosis and lipemia, the patient with Buerger's disease and the patient who developed venous thrombosis and pulmonary in-

farction. In the case of the woman with cyclic thrombocytopenia the disappearance of platelets might have been due to intravascular clotting. On the other hand the progressive increase in activity of stored plasma suggested that the destruction of platelets during storage caused the increased activity. When the platelets were removed by high speed centrifugation, the increase in activity did not occur. The increased plasma activity associated with cyclic thrombocytopenia might then be the result and not the cause of increased platelet destruction.

Increased plasma activity associated with fibrinolysis might indicate intravascular clotting with depletion of fibrinogen and prothrombin. The increased plasma activity in the patient who bled while receiving Dicumarol and who required repeated doses of vitamin K_1 was very interesting particularly as it was later followed by a pulmonary embolus and venous thrombosis. Dicumarol plasma and the Christmas plasma with a similar decrease in activity showed differences when mixed with normal plasma and with plasma showing increased activity. The mixtures which contained Christmas plasma caused the substrate to clot in a shorter time than those containing Dicumarol. The shortest times of all were obtained when the plasma with increased activity was used in the mixture. Because of this difference the term Christmas (P.T.C.) activity should only be used when describing normal or Christmas plasma.

Summary. 1. The thromboplastin generation test was modified by substituting dilute plasma for serum as a source of Christmas (P.T.C.) factor. This modification may broaden the scope of the test and may make it possible to assess increased as well as diminished activity of thromboplastin formation.

2. This method may be used as a quantitative measure of Christmas (P.T.C.) factor activity of normal plasma and plasma from a patient with Christmas disease.

3. The modified test may prove valuable in demonstrating an increased tendency towards thrombosis as well as measuring anticoagulant effectiveness.

4. In both Christmas disease and in Dicumarol-treated patients the plasma has diminished activity in thromboplastin generation. The test demonstrates a distinct difference between the 2 conditions.

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SUMMARIO IN INTERLINGUA

Un Modification Del Test De Generation De Thromboplastina

1. Le test del generation de thromboplastina esseva modificate per le substitution de plasma in forma diluite pro le sero que es normalmente usate como fonte

de factor Christmas. Iste modification promitte extender le applicabilitate del test e permitter le evalutation de augmentos e non solmente de reductiones in le activitate del formation de thromboplastina.

2. Le methodo pote esser usate in le evalutation del activitate de factor Christmas in plasma normal e in plasma ab patientes con morbo de Christmas.

3. Le modificate test promitte esser utile in demonstrar un augmentate tendentia thrombotic e etiam in mesurar le efficacia de anticoagulantes.

4. Tanto in patientes con morbo de Christmas e etiam in subjectos tractate con Dicumarol, le plasma monstra un reducite activitate in le generation de thromboplastina. Le test demonstra un distincte differentia inter le duo conditiones.

SUMMARIO IN INTERLINGUA

(See page 405 for original article)

Le Effecto De Sitosterol Beta Super Le Nivellos Seral De Cholesterol E Lipoproteina In Patientes Qui Recipe Dietas A Basse Contento De Grassia

In un studio "bi-occulte," sitosterol beta esseva administrate a 21 patientes mascule con atherosclerosis patente. Le pesos de omnes habeva essite reducite a nivellos "magre," e illes omnes recipeva dietas a basse contento de grassia. Le droga esseva administrate durante 8 septimanas. Isto esseva precedite o sequite per un simile periodo de administration de un medication fictitie. Le responsa a sitosterol beta monstrava considerabile variationes individual, sed in le nivellos medie del lipoproteinas seral del classes S_f 0–12 e S_f 12–20 grados significative de reduction esseva constatate. Le alterationes de lipoproteina del classe S_f 20–400 e del nivellos de cholesterol seral non esseva significative. Le similaritate de iste responsas de lipido del sanguine con le responsas que occurre sub un regime dietari a basse contento de grassia indica le possibilitate que simile mechanismos es active in le duo situationes e que iste medios de reducer le nivellos de lipido del sanguine es plus o minus additive. Nulle effectos toxic esseva observate in consequentia del diurne administration oral de 10 g de sitosterol beta durante un periodo de 8 septimanas. Le resultatos indica que sitosterol beta ha un definite effecto in reducer additionalmente al minus certes del species de lipoproteina beta in le sero de patientes in qui le nivellos de lipido ha jam essite reducite per medios dietari.

LACTIC DEHYDROGENASE AND GLUTAMIC OXALOACETIC TRANSAMINASE IN NORMAL PREGNANT WOMEN AND NEWBORN CHILDREN*

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The attempts to elucidate the factors responsible for elevation of serum enzymes in disease have also included studies of physiological states such as pregnancy (Brody[2], Hill and Levi[6], and Hill[7]) and growth (Hill[5]). Both elevated (Hill and Levi[6] and Hill[7]) and normal (Brody[2]) levels of serum lactic dehydrogenase have been reported in pregnant women. Some of these conflicting reports have not included the stage of pregnancy studied. Accordingly, in the present study, the lactic dehydrogenase (L.D.) and glutamic oxaloacetic transaminase (GOT) levels have been studied in women in various stages of pregnancy. The levels of these enzymes were normal in all stages of pregnancy, but L.D. levels were found to be elevated in some patients in labor.

Materials and Methods. Lactic dehydrogenase and glutamic oxaloacetic transaminase levels were determined in 70 pregnant women during the different stages of pregnancy (Figs. 1 and 2). In addition, 27 women were studied during labor. The sera in the latter group were collected 2 hours or less before delivery. The women were not studied serially during their pregnancies. The patients' ages ranged from 16 to 36. There were 60% Negroes and 40% Caucasians in the group. Both primigravida and multipara women were studied. Mother's blood was not obtained after delivery. Cord blood from 19 newborn infants was also studied. Fourteen of the latter were from mothers who had been studied during labor.

The L.D. was performed by a method reported elsewhere (Zimmerman and Weinstein[19]). Normal values for this enzyme are below 270 micromols $DPNH_2$ per 100 ml. serum. The GOT was initially performed by the method of Karmen[8]. In the latter portion of the study, the modification of Reitman and Frankel[10] of the method of Umbreit[12,13] was utilized. In the range of GOT values observed in the present study, no significant differences between the results obtained by the 2 methods could be demonstrated. Normal values for this enzyme (GOT) are below 40 units.

Results. Seventy women were studied during one of the trimesters of pregnancy.

In only 2 of these patients were lactic dehydrogenase elevations noted, and these were slight (290 and 305) (Fig. 1). These 2 patients were in the 8th month of pregnancy. Although all other levels were normal, they appeared to be highest during the last trimester. The numbers in each period, however, were too few for statistical analysis. GOT levels were normal in all 70 patients (Fig. 2). Indeed, in patients studied during the first 2 trimesters, the levels were below 15 units.

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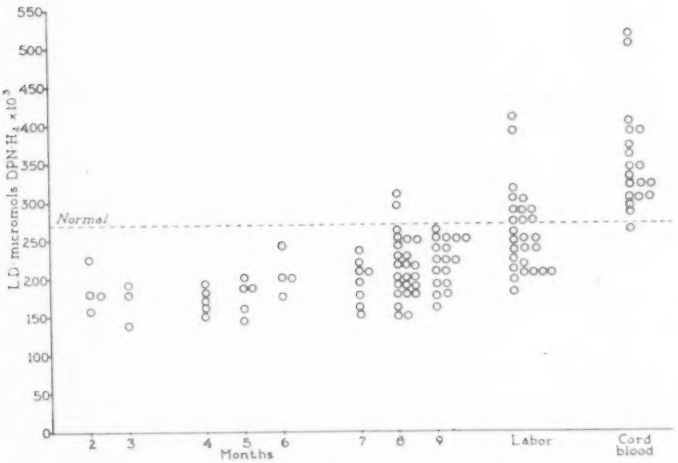

Fig. 1.—Lactic dehydrogenase levels of the serum during the stages of pregnancy, during labor and in cord blood. Each circle represents one patient.

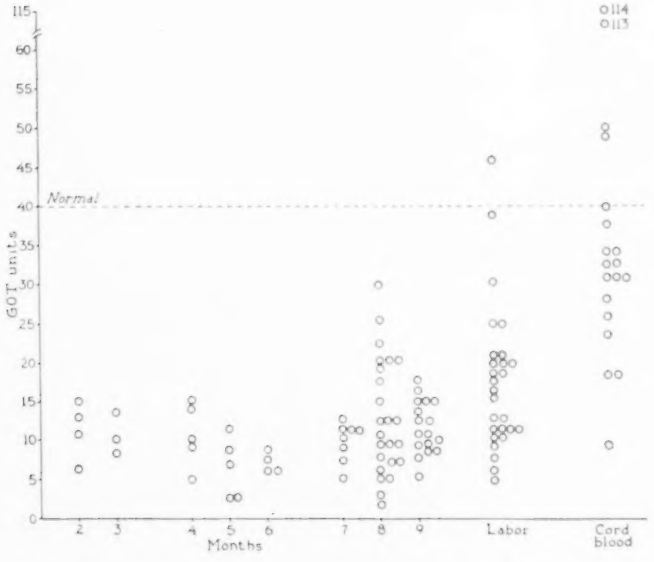

Fig. 2.—Glutamic oxaloacetic transaminase levels of the serum during the stages of pregnancy during labor and in cord blood. Each circle represents one patient.

Studies were performed on 27 women in labor. L.D. levels were moderately elevated in 11 (Fig. 1). The GOT values were normal in all but one (46 units) of the patients in this group (Fig. 2).

Cord blood of 19 newborn infants was studied. The L.D. levels were increased in all but one (Fig. 1). GOT levels were slightly to moderately elevated in 4 instances (Fig. 2). Fourteen of the cord blood specimens were obtained from infants of mothers whose

TABLE 1.—SERUM ENZYME LEVELS OF FOURTEEN WOMEN DURING LABOR AND THE RESPECTIVE CORD BLOOD (SERUM) LEVELS AT THE TIME OF DELIVERY

	Mother in Labor		*Cord Blood*	
Number	*L.D.*	*GOT*	*L.D.*	*GOT*
1.	275	18	530	34
2.	260	9	339	23
3.	175	5	514	26
4.	240	13	320	13
5.	214	11	382	40
6.	212	12	267	18
7.	312	46	335	113
8.	236	16	300	32
9.	213	18	370	48
10.	240	18	285	20
11.	298	20	360	50
12.	240	20	380	38
13.	217	25	320	31
14.	230	18	325	33

serum enzyme levels had been studied during labor. In all, the enzyme levels were higher in the cord blood than in the maternal blood (Table 1) except for one instance (Table 1, #4) in which the GOT levels were the same in both the newborn infant and its mother.

Discussion. In the present study, pregnancy did not appear to be associated with elevated levels of lactic dehydrogenase. In only 2 of the 70 patients studied, in all trimesters of pregnancy, were there L.D. elevations, and these were minimal. L.D. elevations appeared more frequently during labor. Even in this group most of the elevations were moderate. In the published reports (Hill[5] and Hill and Levi[6]) of elevated L.D. levels in pregnancy, the stages of pregnancy were not indicated. In the recent study of Brody[2] of 10 patients representing all 3 stages of pregnancy, the L.D. levels were stated to be normal. The results of the present study of 70 patients are consistent with the latter report.

GOT elevations were not observed in the mothers during pregnancy or labor. One borderline elevation (46 units) was noted during labor. The low (but normal) levels of GOT observed during the first 2 trimesters confirm the observations of low transaminase levels in pregnancy reported by Bowen, Wroblewski, and LaDue[1].

The almost uniformly elevated levels of L.D. in cord blood have not, to our knowledge, been reported before. Lactic dehydrogenase levels have been reported (Hill[5]) to be approximately twice normal during the first year of life and to be higher in children than in adults.

In a recent study (Kove, Goldstein and Wroblewski[9]), the normal range for GOT in the serum of neonatal infants was reported to be 13 to 120 units and in that from cord blood to be 20 to 54 units. In the present study, the cord blood serum of 17 of the 19 infants showed values below 52 units. The GOT serum levels in the 2 other cord blood specimens were 113 and 114 units respectively.

Although the serum values for L.D. and GOT of the cord blood were consistently higher than those obtained from the respective mothers during labor, it should be emphasized that maternal and fetal specimens were not simultaneously obtained. Nevertheless, it seems reasonable to conclude that

L.D. and GOT levels are higher in infant serum than in that from the normal adult. Glendening, Cohen and Page[4] have demonstrated that whole blood transaminase is higher in the fetus than the mother. Similarly, elevations of the serum isocitric dehydrogenase levels in cord blood have been reported by Wolfson and Williams-Ashman[18]. These elevated enzyme levels might reflect a different rate of metabolism in the fetus than in the adult, increased liberation of enzymes from tissues, or both.

Lowered levels of transaminase in the blood of pregnant women have been ascribed to pyridoxine deficiency (Glendening, Cohen and Page[4]). Pyridoxal phosphate is the coenzyme necessary for transaminase activity (Snell[11]). There are several observations suggesting a defect in pyridoxine metabolism in pregnancy (Wachstein, Gudaitis and Lobel[14,15,16]). Recently, it has been shown that the levels of pyridoxal in the circulating leukocytes of pregnant women are abnormally low, while those of the fetus are higher (Wachstein, Moore and Graffeo[17]). The lower levels of transaminase activity in late pregnancy may, therefore, reflect the lack of coenzyme rather than low levels of enzyme (apoenzyme).

Summary. 1. The lactic dehydrogenase and glutamic oxaloacetic transaminase levels were studied in 70 women representing the 3 stages of pregnancy. Two slightly elevated lactic dehydrogenase levels were noted. No glutamic oxaloacetic transaminase elevations were found. In fact, the glutamic oxaloacetic transaminase levels of this enzyme were generally lower than the average adult level.

2. Twenty-seven women were studied during labor. Eleven of these patients had elevated L.D. levels, only 2 of which were marked. Only one borderline transaminase elevation was noted in this group.

3. Cord blood from 19 infants was studied. The lactic dehydrogenase levels were elevated (above 270) in the cord blood in 18 of 19 newborns studied. The transaminase levels ranged from 9 to 52 in 17 of these. In the remaining 2, the levels were 113 and 114 units respectively.

ACKNOWLEDGMENT: We are grateful to Dr. William F. Mengert, Chairman of the Department of Obstetrics and Gynecology, University of Illinois School of Medicine for his cooperation in this study and to Dr. Robert E. Kay for his assistance in obtaining the specimens.

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SUMMARIO IN INTERLINGUA

Dishydrogenase Lactic E Transaminase Glutamic-Oxalacetic In Normal Gravidas E Neonatos

1. Le nivellos de dishydrogenase lactic e de transaminase glutamic-oxalacetic esseva studiate in 70 feminas qui representava le 3 stadios del pregnantia. Duo levemente elevate nivellos de dishydrogenase lactic esseva notate. Nulle elevationes de transaminase glutamic-oxalacetic esseva constatate. De facto, le nivellos de iste enzyma esseva generalmente infra le valor medie pro adultos.

2. Trenta-septe feminas esseva studiate durante lor labores. Dece-un de illas habeva elevate nivellos de dishydrogenase lactic. Iste elevation esseva marcate in solmente 2 casos. Solmente un caso de elevation liminal de transaminase esseva notate in iste gruppo.

3. Specimens de sanguine ab le cordon umbilical esseva studiate pro 19 infantes. Le nivellos de dishydrogenase essseva elevate (e supra 270) in 18 del 19 casos. Le nivellos de transaminase variava inter 9 e 52 in 17 del 19 casos. In le remanente 2 casos, le nivellos esseva 113 e 114 unitates, respectivemente.

MANAGEMENT OF MUSCLE SPASM ASSOCIATED WITH TRAUMA RESULTING FROM AUTO ACCIDENTS

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Injuries to the spine and spinous processes have been seen with increasing frequency. Automobile accident statistics have revealed an unmistakable correlation between accident rate and number of paravertebral injuries.

Automobile accidents can produce both physical and emotional trauma. Persistent pain has occurred, even from minor injuries, where there has been no roentgenologic evidence of damage to the paravertebral structures. There has been an accurate correlation between the persistence of pain and local muscle spasm. Also the duration and variable intensity of muscle spasm may be influenced by the degree of psychic stress and anxiety-tension associated with the accident.

Conventional therapeutic measures and routine physical therapy have limitations. The usual methods of treatment, such as the application of heat and the use of pain relievers, have proven far less effective in patients where psychic disturbances have been most marked. In instances where the emotional imbalance has persisted for weeks, the inadequacies of the standard method of treatment have been most obvious. Therefore, in those cases where physical trauma has been minimal and psychogenic disturbances have been pronounced, the ideal therapeutic objective would be the proper management of both muscle spasm and emotional distress. Meprobamate* has been reported to be a useful drug for this purpose (Fazekas, Shea and Sullivan[2]). Pharmacologic studies have indicated that the drug acts on the central nervous system to produce relaxation of peripheral muscle and alleviation of anxiety and tension (Berger[1], Fazekas, Toupin and Alman[3], and Perlstein[4]). Unlike such related compounds as mephenesin, meprobamate has been found to be relatively long acting (Smith[5]). Following its oral administration, its peak effect may be reached in 30 to 60 minutes (Smith[6]), and is maintained for about 6 hours thereafter.

Plan of Study. Twenty-six patients with typical symptoms of paravertebral injury resulting from varied trauma, were selected from patients seen in private practice by the authors. Ages ranged from 16 to 56 years, with a median of 36 years. Twelve patients were male and 14 were female. Table 1 lists the primary diagnoses.

Patients began meprobamate therapy when first seen after the accident. A standard dose, 400 mg., 4 times daily, was given for periods ranging from 3 to 21 days. Mean duration of therapy was 11 days. Supplemental therapy was restricted to symptomatic treatment of the injury with local heat, rest, physical ther-

*Meprobamate (2-methyl-2-propyl-1,3 propanediol dicarbamate) is available from Wyeth Laboratoris, Inc., Philadelphia Pa., as Equanil.

apy where indicated, and such analgesics as phenacetin, codeine, and the salicylates. One patient also received conjugated estrogens.

Response to meprobamate therapy was graded from 1-plus to 4-plus. Three factors entered into the final response tabulated: (1) effect of meprobamate on muscle spasm, (2) effect of the drug on pain induced by muscle spasm, and (3) its effect on emotional tension and distress.

TABLE 1.—RESPONSE TO MEPROBAMATE THERAPY IN 26 PATIENTS WITH TRAUMATIC PARAVERTEBRAL INJURY

Diagnosis°	*Number of patients showing the diagnosis*	*Clinical Response* 4+	3+	2+	1+
Mild cerebral concussion	2	2	—	—	—
Cervical spine injury (whiplash)	13	12	—	1	—
Cervicothoracic injury	3	3	—	—	—
Thoracic spine injury	2	25	—	—	—
Lumbosacral injury	12	8	3	1	—
Joint sprain	5	3	1	1	—
Total	(37)	30	4	3	—
Percentage response		82%	10%	8%	—

°Includes 17 patients with a single diagnosed paravertebral disorder, 7 patients with 2 diagnosed disorders, and 2 patients with 3 diagnosed disorders.

A 4-plus evaluation was assigned only if clinical examination showed complete skeletal muscle relaxation, pain was minimal or absent, and no signs of emotional anxiety or distress were perceived. A 3-plus response was tabulated if muscle relaxation appeared complete, but mild, well-tolerated pain persisted or mild emotional tension, or both, remained. In 2-plus responses, definite improvement was noted; sufficient muscle relaxation was induced to encourage rapid healing of the injury, but some pain or emotional anxiety, or both, remained. A 1-plus improvement indicated mild improvement.

Degree of skeletal muscle relaxation was determined by clinical evaluation. Magnitude of the reflex spasm on extension of the injured muscle group was noted. Tenderness on palpation and range of motion also entered the evaluation.

Because analgesics also were administered at times in this study, pain relief was not considered a reliable factor in patient response to meprobamate. However, where reduction of pain appeared clearly associated with administration of the muscle relaxant agent, it was noted.

Emotional tension, or its lack, was evaluated in relation to the degree of distress present after the accident, but before administration of meprobamate. A careful history gave some clue to the patient's underlying emotional tension prior to the accident.

Results. Table 1 lists the symptomatic response to meprobamate of 37 disorders observed in 26 patients. Expressed in number of patients, and considering only primary diagnoses, 19 of 26 cases showed a 4-plus response, and 23 of 26 showed a 3-plus or better response. The following case histories demonstrate average or less-than-average improvement.

Case Reports. CASE 1. A primiparous white housewife, aged 25, first seen on November 14, reported injury by an automobile 3 days before, stating that she was struck and knocked down by the open door of her own vehicle as it rolled backward down a hill.

At time of examination, the patient was markedly nervous and agitated. She complained of severe generalized headache; stiffness and soreness of the shoulders with pain radiating into the low cervical region; pain in the lower left quadrant, aggravated by bending, coughing, or sneezing; severe pain in the lumbodorsal spine; pain in the left leg, particularly in the upper thigh; and pain and limited motion of the left ankle. Physical examination showed multiple abrasions and bruises over the right and left ankles, calves, knees and thighs, left buttock and shoulder and the right hand. The patient limped on the left leg. Bending forward or rising from supine to sitting position caused pain.

Muscle spasm was observed in the cervical region with midline tenderness over the 5th and 6th cervical vertebrae. Tenderness and muscle spasm existed also over the entire dorsal spine, with limited flexion both anteriorally and laterally. Percussion of the lumbosacral spine was painful. Complete neurologic examination was negative. Roentgen

studies of the skull, lumbar spine and pelvis performed at this time did not reveal definitive bone injury, although a moderate left-sided scoliosis of the lumbar spine existed.

The patient was confined to bed with instruction to use local heat for relief of back pain. She slept on a bedboard. Analgesics, sedatives and meprobamate were prescribed. When seen at home on November 15, she was alert and relatively free of pain other than over the lumbosacral spine. Muscle spasm was absent.

Further roentgenograms of the spine revealed an anterior compression centered over the 10th thoracic vertebra with some apparent wedging of the 9th and 11th vertebrae as well. The patient was hospitalized the following day with a diagnosis of anterior compression fracture of the dorsal spine and mild cerebral concussion.

Before dismissal from the hospital on November 23, 1956, she was fitted with a high-back corset support. The patient understood immobilization in this garment would be required for at least 3 months, and in that time she was to avoid bending, lifting, or straining. On November 28, the patient was seen at home with edema and pain in her left leg. With bed rest and elevation, symptoms subsided within 48 hours. When last seen in the office on December 3, she wore her back support and was relatively free of pain. Meprobamate therapy was discontinued at that time.

CASE 2. A white male officeworker, aged 46, was seen in private practice on January 28, several hours after injury resulting from an automobile collision. The patient stated his automobile was suddenly smashed from behind by a second car. He was thrown forward; his body struck the steering wheel as his neck snapped backward. Transient loss of consciousness was followed by a dazed period.

The patient reported severe generalized headache and a burning pain extending from left shoulder to left fingertips. Positive findings at examination included (1) multiple contusions and abrasions of the chest, (2) limitation of neck motion in all directions, (3) limited motion of the left shoulder, particularly in abduction and internal rotation, and (4) extreme weakness in grasp of the left hand. Roentgenograms of the thoracic spine revealed a marked scoliosis, convex to the right at the 6th thoracic vertebra and convex to the left at the 9th vertebra. The 9th thoracic vertebra showed prominent wedging at the right lateral margin which had a 1.0 cm. opening versus a 2.5 cm. opening on the margin of the left border.

The diagnosis was mild cerebral concussion and whiplash injury of the cervical spine with secondary traumatic injury of the lower brachial plexus and ulnar nerve.

Therapy consisted of analgesics, meprobamate, local heat and exercise. On this regimen, the patient's discomfort partially cleared over the next few days. Headache, neck pain and left arm symptoms continued, although they were more tolerable. The patient complained for the first time of numbness and coldness of the left arm.

The patient remained incapacitated from January 28 through February 15, when meprobamate was discontinued. A lighter work schedule has been necessary since that time. All symptoms continued to diminish in succeeding months. When last seen on June 4, the patient complained of occasional generalized headache, slight neck tenderness and persistent mild pain and numbness in the left arm. Further progress is to be expected.

Of 3 patients developing 2-plus (fair) responses, one male not only had cervical and lumbosacral injury, but also extensive and painful contusions and abrasions. A second patient with a 2-plus response also received conjugated estrogen therapy.

Drowsiness was the only side effect noted. In 6 patients who developed mild to moderate sleepiness, reducing the dose of meprobamate corrected the condition. Where the full dose was necessary for complete muscle relaxation and drowsiness also resulted, the sleepiness tended to disappear after several days of medication.

Comment. In this study, meprobamate both relieved muscle spasm and reduced anxiety and distress in all patients. In 23 of 26 patients, skeletal muscle relaxation appeared complete. It is our clinical impression that meprobamate contributed to reduction of pain through its antispastic and anti-anxiety effect. Meprobamate in our small series proved a valuable aid in the early management of muscle spasm associated with injury resulting from accidents.

Summary. Meprobamate was administered as an adjunct to treatment of 26 patients with acute paravertebral injury resulting from accidents. The drug relieved muscle spasm adequately in all cases, and assuaged anxiety and distress caused by the traumatic experience.

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SUMMARIO IN INTERLINGUA

Tractamento De Spasmo Muscular Associate Con Trauma Como Resultato De Accidentes De Automobile

Meprobamato esseva administrate como adjuncto al tractamento de 26 patientes con acute vulneres paravertebral resultante de accidentes. Le droga alleviava spasmos muscular de maniera adequate in omne le casos e calmava le anxietate causate per le experientia traumatic.

CLASSIC HEMOPHILIA IN A NEGRO INFANT

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Since the introduction of the thromboplastin generation test in 1953 by Biggs and Douglas[1], it has been possible to classify hemophilic diseases as deficiencies of either plasma, serum or platelet factors. Classic hemophilia is defined as a specific deficiency of a labile plasma factor commonly called anti-hemophilic globulin.

Hemophilia in the Negro race is extremely rare; the disease has been reported only 29 times (Bullock, Johnson and Davis[2], and Nesbitt and Richmond[5]). However, the first 4 were probably not true classic hemophilia since the disease was reported in females and in a male whose father had a bleeding tendency. Briefly, it may be stated that hemophilia is transmitted as a sex-linked recessive trait (Quick[6]).

This is the first report of classic hemophilia in the Negro race which has been definitely established by the thromboplastin generation test.

Methods. Clotting times, prothrombin times, serum prothrombin times (one stage), recalcification times, and thromboplastin generation tests were done by described methods (Biggs and Douglas[1] and Tocantins[8]). The bleeding time was done by the method of Duke.

Case Report. G.M., a colored male infant, was a full term spontaneous delivery at Jackson Memorial Hospital, January 31, 1956. There was no obstetrical instrumentation and no physical abnormalities noted at birth. The patient was noted to bleed excessively from his circumcision 2 days after birth. Bleeding stopped with pressure dressings.

At the age of 7 months, the patient accidentally lacerated his upper lip. This was treated with a catgut suture, but because of persistent bleeding and oozing, the patient was admitted to the hospital and physical examination was within normal limits, except for the small sutured laceration of the upper lip and marked pallor of the mucous membranes and nail beds. The patient's hemoglobin was 3.3 gm. and his hematocrit was 18%. He was treated with transfusions; the bleeding stopped in 6 hours and he was discharged. One week later, the patient was again admitted to the hospital because of recurrent bleeding from his upper lip. On this admission, the bleeding persisted despite frequent transfusions.

The following laboratory data was obtained: The hemoglobin was 10 gm., platelets numbered 126,000 per c.mm., the plasma prothrombin time was 12 seconds, the serum prothrombin time was 12 seconds, the bleeding time, 3 minutes, and the coagulation time was prolonged to 90 minutes. The thromboplastin generation test showed a plasma defect which was corrected by normal plasma, but was uncorrected by known hemophilic plasma (see Fig. 1). The patient was treated with fresh frozen plasma with prompt stoppage of the bleeding and he was subsequently discharged after 3 days. In the intervening 6 months, the patient has been seen frequently in the emergency room because of frequent subcutaneous hematomas which have responded to symptomatic treatment, and a transfusion on one occasion. At 2 intervals over the past 6 months repeated coagulation studies of the patient's blood have confirmed the diagnosis of hemophilia.

The history elicited no familial bleeding tendency or hemophilia-like diseases. However, it was noted that the patient's great-

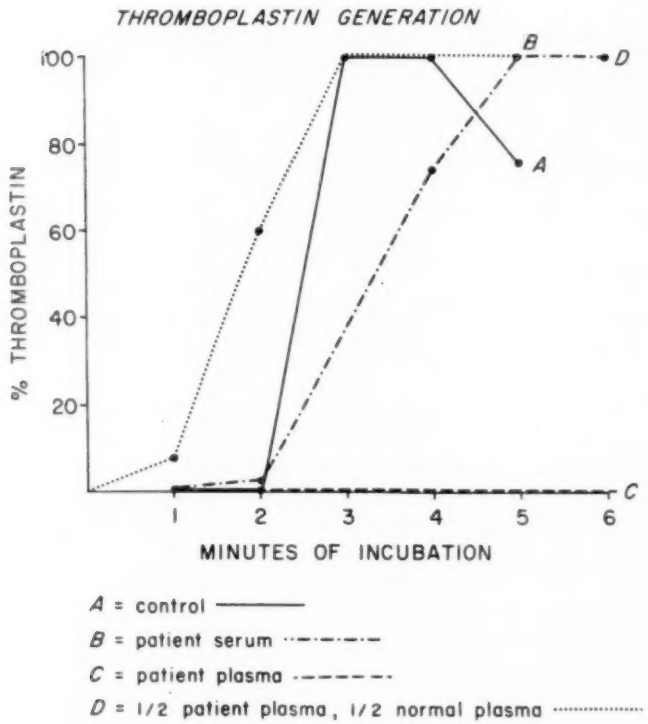

Fig. 1.—The following mixtures were used in the thromboplastin generation test:
(A) normal serum, normal plasma and suspension of brain phospholipid
(B) patient's serum, normal plasma and suspension of brain phospholipid
(C) patient's plasma, normal serum and suspension of brain phospholipid, and
(D) ½ volume of normal plasma, ½ volume of patient's plasma, normal serum and suspension of brain phospholipid.

TABLE 1.—COAGULATION STUDIES OF THE PATIENT AND HIS FAMILY

	Clotting time in minutes	*Prothrombin time in seconds*	*Serum Prothrombin time in seconds*	*Recalcification time in minutes*
1. G.M. (Patient)	140	13	13½	10
2. D.M. (Mother)	20	12½	34	2½
3. N.W. (Grandmother)	20	12½	27	2½
4. L.L. (Male cousin)	28	13	32	3
5. T.W. (Female cousin	—	12½	—	2¾
6. L.A.L. (Female cousin)	30	13	45	2½
7. V.W. (Aunt)	20	13	50	2
8. L.M.L. (Aunt)	30	13	33	2
9. A.W. (Aunt)	28	12½	30	2½
10. J.W. (Uncle)	23	12	29½	2
11. S.W. (Uncle)	22	12	32	2

grandmother had 10 stillbirths, 2 of which were females and 8 of which were males. There were 3 normal females born to the patient's great-grandmother. The patient's grandmother also had 5 stillbirths, all males. There were 4 normal females and 2 normal males born to the patient's grandmother. The patient's mother had no known bleeding tendency. However, the patient's cousin died in Jackson Memorial Hospital at the age of 10 months because of bleeding into his brain of unknown etiology. Examination of the cousin's chart revealed that he had bled for several hours before death following a pin prick to his finger for a routine blood count. The cousin had died shortly after admission to the hospital and necropsy revealed a massive bleeding into the brain without apparent cause. Postmortem bone marrow was normal. Coagulation studies of all living members of the patient's family were within normal limits (see Table 1). The patient's family tree is illustrated in Fig. 2. It was assumed that all of the male stillbirths in the family tree were the result of bleeding from hemophilia.

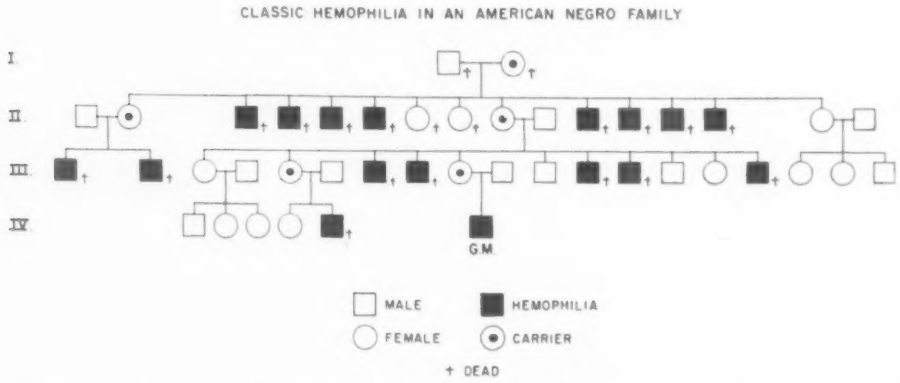

Fig. 2.—The maternal family tree of the patient is shown with the probable mode of transmission of the disease.

Discussion. A recent review (Bullock, Johnson and Davis[2]) of the literature pointed out that there were only 15 authentic cases of hemophilia reported in Negro subjects, and they added 14 more cases of their own. However, in only 7 patients were sufficient studies done to establish that the defect was due to absence of anti-hemophilic globulin. Several instances of Christmas Disease (serum defect in thromboplastin formation) have been reported (Lewis and Ferguson[4]) in the Negro. It is quite reasonable to expect that some of the reported instances of hemophilia in Negro subjects may really be Christmas Disease.

It is interesting to note that in a recent report (Ratnoff and Margolius[7]) on the epidemiology of hemophilia and Christmas Disease, no mention is made of the racial incidence of these diseases. In the Greater Miami area, there are 30 hemophilic families and of these there are 3 families with Christmas Disease. All of the families are of the white race except for the family presented in this paper.

Summary. A case of proven hemophilia due to specific deficiency of the plasma factor, anti-hemophilic globulin has been described in a Negro infant. This report emphasizes the fact that hemophilia can occur in the American Negro, and probably with greater frequency than has been suspected from the literature.

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SUMMARIO IN INTERLINGUA

Hemophilia Classic In Un Infante Negre

Es describite le caso de un infante negre con provate hemophilia causate per un carentia specific del factor plasmatic globulina anti-hemophilic. Le reporto insiste que hemophilia pote occurrer in negros american e que su frequentia in negros excede probabilemente lo que on supponerea super le base del litteratura.

PROGRESS
OF
MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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THE MOUTH IN CERTAIN DISEASES OF THE SKIN

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COINCIDENTAL involvement of the mucous membranes of the mouth occurs in a number of diseases of the skin. A considerable amount of confusion as to diagnosis, attends the viewing of some lesions in the mouth, with added confusion when attempting to arrive at an early diagnosis. However, the concomitant presence of cutaneous lesions when lesions of the mouth exist, lessens the confusion. It is the scope of this survey to include only those diseases affecting the oral mucosa that have a relationship to certain diseases of the skin, either occurring in the absence of the cutaneous changes or in conjunction with them. It is difficult to put into a specific classification those diseases to which I have reference. Only those oral lesions that are related to diseases of the skin, and as yet are "hopelessly" moving in a space-orbit of unknown etiology, will be considered here.

The lining of the mouth is a modified stratified epithelium which is continuous with the skin. Pillsbury, Shelley and Kligman[48] stated that it is not unusual that some disorders which are described as skin diseases should also affect the oral cavity. Oral lesions have their counterpart in lesions of the skin, but because of wetness, friction of the parts and warmth, the lesions of the mouth are modified and the objective signs or appearances may vary considerably from the appearance of the processes on the skin. However, the identity of histopathological changes is usually retained. The knowledge that some lesions in the mouth may be accompanied by lesions of the skin should encourage the examiner to make a thorough search of the cutaneous

integument. Awareness of the characteristics of certain diseases of the skin should likewise necessitate the search for these characteristics and to couple the findings with the findings in the mouth in order to establish a correct diagnosis.

Lichen Planus. Burkett[13] was of the opinion that in about 50% of the cases of lichen planus oral lesions were present. He maintained that the incidence of lichen planus limited to the mouth was greater than generally appreciated and that less than 10% of the cases seen because of lesions in the mouth had or complained of skin lesions. He stated that dermal lesions are uncommon in patients with primary oral lesions of lichen planus so that they are of little assistance in making a positive diagnosis. I am not in accord with this view since dentists, who often may be the first to see oral lesions of lichen planus, are rarely afforded the opportunity to examine the entire body for evidence of cutaneous lichen planus on sites of which the patient has been unaware. This would particularly be the case should subjective symptoms be absent in lichen planus of the genitalia of women, especially of the vulva, where, like the frequent involvement of the penis in the male, lesions are often characteristically found. Schraff[53] was of the opinion that in 26% of the cases of lichen planus oral involvement was primary.

Lichen planus is a chronic inflammatory dermatosis consisting of small, flat-topped, angular or polygonal papules, often showing a variation of color from deep red to violaceous hue, the surface of the lesions usually marked by striae and the center depressed or umbilicated. The eruption, most often chronic, may be acute, and, most often limited to certain regions, it may be general in type. The disease most frequently affects the flexor surface of the extremities, the genitalia and the mucous membranes of the mouth. The cause is unknown, though a viral etiology has been given some support. Many observers have favored psychosomatic factors as a cause of the disorder. Burkett[13] has observed lichen planus in patients suffering from long-standing vitamin B deficiency. Oral lesions may first be discovered by a dentist in patients complaining of roughness on the cheek or palate, but most commonly the lesions are found on the mucosa of the cheeks opposite the molars. The lesions most frequently consist of interlacing, poorly-defined bluish-gray lines of a spider web pattern, raying outwards. Where the lines cross each other, small elevated points can be seen. Sometimes purplish angular papules can be found. Sometimes a diffuse washed-out whitish leather appearance is seen, pseudomembranous in type. Any part of the oral mucosa may be affected. Anderson[3], as well as other authors, reported lichen planus of the gums[16]. Thomson[62] described a patient with a sore throat who had pain on swallowing. The tonsils showed typical lesions of lichen planus. The diagnosis was confirmed by finding typical hypertrophic lichen planus lesions on the neck, scalp and forearm. The buccal mucosa and tongue were normal.

Involvement of the lower lip is not uncommon, and here the picture may take on the appearance of a fine network of purplish-white lines. Sometimes, a sharply circumscribed, dry, whitish patchy lesion may exist, somewhat resembling leukoplakia[15]. The cutaneous counterpart of umbilication in individual lichen planus is not too frequently seen on the buccal mucosa, but if keen attention is paid to the criss-crossing points of the wider spider lines, the umbilication can be made out. Upon the dorsum of the tongue,

patches of lichen planus not infrequently show delling of the papules. Involvement of the vermilion borders of the lips is not uncommon. Most frequently, the lower lip is involved and here is seen the closest counterpart of lichen planus as it affects the skin[45]. Lesions frequently show the typical characteristics of polygonal, angulated, flat-topped, violaceous and centrally umbilicated papules, though with a whitish, dry and adherent scale, and with striking striae of Wickham.

Frequently, erosive lesions, superficial in type, can be the predominant feature of oral lichen planus. They may appear as herpetic lesions, but these are often surrounded by the typical telltale spider-web lines. Burkett has seen erosive lesions undergo remissions and exacerbations, the latter at times associated with emotional disturbances or a menstrual period in the female. Sometimes superficial, eroded and ulcerated lesions appear which may be suspected of being syphilitic, tuberculous, or carcinomatous.

The principal diseases which should be differentiated from lichen planus of the mouth are leukoplakia, moniliasis (thrush) and syphilitic mucous patches.

Psoriasis. A considerable amount of controversy concerned the existence of psoriasis of the mouth in the past. In recent years psoriasis has been accepted as a disease which may affect the buccal mucosa, though uncommonly. Psoriasis is a chronic, recurrent disease of the skin of unknown etiology which is characterized by an eruption of reddish, flat papules or circumscribed plaques or patches of varying size, covered with silvery, lamellated scales. Sutton[60] stated that the mucous membranes are seldom involved and Norins and Yaffee[46] commented that psoriasis of the oral mucous membranes must be uncommon if not rare. No instance of psoriasis limited to the mouth has been reported. In the sparse number of recorded cases in which lesions have appeared orally and corroborated by histopathological findings, they have been accompanied by characteristic lesions of the disease on the skin. Buccal and lingual lesions have been said to occur as superficial, sharply circumscribed, red or whitish plaques, oval to round and somewhat resembling the moist secondary syphilid[67]. Becker and Ritchie[5] reported the case of a 22-year-old woman who had psoriasis since 5 years of age and buccal lesions since childhood. On the buccal mucosa, at the oral commissures and extending half the distance to the third molars, the epithelium was thickened and desquamating. The denuded surface was deeper red than the normal mucosa. The thickened plaques were loosely adherent. They pointed out that the features suggesting buccal psoriasis were: the appearance of the lesions during childhood, the absence of syphilis, absence of irritating factors such as might account for leukoplakia, the desquamation of the epithelium in loose lamellae, the rapid change of the clinical picture, the nature of the histological changes and the presence of psoriasis on the cutaneous surfaces. It was their opinion that the questionable occurrence of psoriatic lesions of the mouth, as so diagnosed, was located in the "cutaneous" region of the cheek, a linear region from the oral commissures to the wisdom teeth.

Usher[65] described 2 cases of psoriasis of the mucous membranes. In one, a man with cutaneous psoriasis, the tongue was affected from the circumvallate papillae posteriorly to the tip anteriorly, the sides and the under surface also being affected. The lesions were from minute split-pea size papules to about ½ inch, were round and

sharply demarcated and with little tendency to fuse. The papules were covered with a superficial layer of gray-white epithelium which could be easily scraped off leaving prominent papillae. On the under surface of the tongue, on each side of the midline was a sharply circumscribed, large, oval plaque extending from the tip to the attachment posteriorly. The plaques were red and denuded of the surface epithelium. In the other case, a girl of 13 who had psoriasis for 3 years, there was extensive involvement of the buccal mucosa from the anterior commissures to the anterior fauces posteriorly. There was a fairly coarse interlacing network of grayish-white striae enclosing the unaffected mucous membrane. The papules were only slightly raised above the unaffected parts, and the epithelium could be scraped off only with difficulty.

Norins and Yaffee[46] described a case of psoriasis of the hard palate in a 61-year-old man who had a chronic, widespread psoriasis of the skin. Some 7 years prior, he had complained of hoarseness for 6 months and had shown a glossitis accompanied by a dusky erythema of the oral, pharyngeal and laryngeal mucosa. On the occasion of his latest examination, the buccal cavity showed a mottled, dusky erythema involving the hard and soft palate, biopsy of which showed a histological picture compatible with psoriasis, namely, parakeratosis, thinning of the supra-papillary epidermal plates and elongated rete ridges with clubbing. Goldman and Bloom[29] described 2 cases of oral manifestations of psoriasis. In one, a 63-year-old man who had psoriasis of the skin, there was an asymptomatic, slight thickening of the mucosa of the lower lip of 2 months' duration, consisting of a moderately indurated, raised, grayish-white, irregularly shaped plaque to the left of the midline. In the other case, a 28-year-old man with psoriasis of the scalp had an irregular, whitish-gray, fuzzy, raised lesion on the floor of the mouth extending diffusely posteriorly. In both instances the histological findings were comparable to those of cutaneous psoriasis, except that Munro's abscesses were not present. Similar changes involving the gums have been described[12].

The vermilion parts of the lips are the only portions of the mouth that can be said to assume, partially, the clinical counterpart of psoriasis of the skin. In acute psoriasis, particularly of the generalized guttate variety, the external lips may show a diffuse or patchy whitish-yellow scaling, frequently with secondary superficial fissuring. Chronic lesions often assume a picture not unlike superficial keratoses of the lip. Isolated or confluent islands of dry micaceous-scaling may occur, the scales more easily removable than those of keratoses. The vascularity of the lips and the ease of bleeding mask the detection of capillary hemorrhage (Ausspitz sign) when the scales are scraped off.

An almost constant feature of oral psoriasis is the clearing of the lesions concomitant with clearing of the cutaneous lesions.

Pityriasis Rosea. Pityriasis rosea is an acute, rarely chronic, inflammatory dermatosis which is characterized by a self-limited eruption consisting of yellowish pale-red, superficial scaling, maculopapular patches of varying size, usually round, oval or circinate, and distributed chiefly over the trunk and extremities, frequently along the cleavage lines. Only in recent years have dermatological textbooks mentioned the existence of oral mucous membrane lesions in cases of pityriasis rosea. Guequierre[31] presented a case in 1938 in which the correlation between the

pityriasis rosea and the oral lesions was questioned at the time, but 3 years later he and Wright[32] published a summary of 14 cases with oral lesions. The realization that mouth lesions of pityriasis rosea can exist during an attack of the disease is additionally strengthened by the report of 4 cases by Greenbaum[30]. In a case reported by Costello[18] lesions appeared during a febrile state accompanying the cutaneous eruption.

The oral lesions of pityriasis rosea have been described as dark red, round maculopapules on the cheeks which undergo early desquamation with a dirty-grayish appearance. Punctate hemorrhagic lesions have also been observed[30,32,50]. The oral lesions have been noted to be most marked during the first week of the generalized cutaneous eruption, usually within 10 days. A generalized catarrhal stomatitis with increased salivation may precede the more specific mucosal lesions according to Burkett[13]. Rosenbaum described a case[51] of a 28-year-old man who complained of constipation and a bitter taste in the mouth 3 days before he was seen with a generalized pityriasis rosea. The patient did not know how long his eruption had been present.

The more specific mucosal lesions consist of small, round, raised, slightly elevated, painful lesions on the cheeks in the molar region along the interdental line. Eroded areas similar in appearance to measles may develop in the central portion of the lesions. In Rosenbaum's case[51] 8 to 10 dark red, discrete, pinpoint to pinhead-sized lesions were found on the soft palate. Four days later, 2 small, sharply circumscribed, hemorrhagic lesions appeared between the pinpoint lesions. These hemorrhagic lesions increased in size during the next few days, reaching a maximum diameter of 7 and 5 mm. respectively. The lesions rapidly regressed and 5 days before the disappearance of the cutaneous lesions, they had completely healed. He found no difficulty in ruling out avitaminosis C, thrombocytopenic purpura, influenza, Osler's disease and gonococcemia, and regarded the mucous membrane lesions of pityriasis rosea as an enanthem of the disease in which the enanthem appeared at the height of the disease and regressed before the skin lesions disappeared.

Pityriasis rosea is a relatively common skin disease, yet of 270 cases observed by Vass[66], oral lesions were found in only one case, and the case reported by Rosenbaum was the first in 300 cases. However, this low incidence may be attributed to the fact that the mouth is often not examined in patients having pityriasis rosea unless subjective symptoms exist in the oral cavity. On the other hand, otolaryngologists or dentists to whom patients may first go because of lesions in the mouth, may not examine for evidence of cutaneous pityriasis rosea, and patients may not reveal to the examining physician the existence of a sparse number of lesions for which they may have little concern.

Erythema Multiforme. Erythema multiforme has been variously defined as an acute, inflammatory disease characterized by bright to purplish-red macules, papules, nodules, vesicles or bullae which vary greatly in size, configuration and grouping, and with a tendency to recurrence. As originally described by Hebra, erythema multiforme was considered to be a comparatively simple disease, usually limited to the hands, forearms, face and neck, which runs its course in 2 to 4 weeks and is commonly recurrent and of unknown origin[47]. As a symptom complex, erythema multiforme can occur as a symptomatic erythema of many diseases of known infectious nature, as a

cutaneous expression of visceral disease or as an allergic reaction produced by the ingestion of many different drugs or the injection of various parenteral medicaments or sera. A form of erythema multiforme exists in which the eruption is of such severity that difficulty is experienced in distinguishing it from certain forms of pemphigus.

It is the feeling of this writer that those cases yielding a clinical picture of erythema multiforme that are found to result from absorption of toxic products be designated as a "toxic erythema" and that those cases developing as a result of drug sensitivity be designated as "dermatitis medicamentosa." Accordingly, if there is oral involvement to designate them as "toxic stomatitis" or "stomatitis medicamentosa," respectively. In this way, such cases could easily be differentiated from the original erythema multiforme concept: a disease recurrent in nature and of an unknown etiology.

Involvement of the mouth in erythema multiforme is not infrequent, the disease occurring independently of any cutaneous eruption[14] or in conjunction with lesions on the skin. Lesions in the mouth may precede the cutaneous eruption or they may occur simultaneously with it. Erythematous or hyperemic macular or papular lesions may arise anywhere on the buccal mucosa or tongue, and these are usually transitory in nature. As the disease progresses, vesicular or bullous lesions develop at the sites. Frequently erythematous elevated areas of various size and shape may make their appearance, usually with a slightly raised yellowish-white coating. Rosenberg and Rosenberg[52] have described such an involvement accompanied by a conjunctivitis. Similar changes were described by Ageloff[2]. It is not unusual for oral symptoms to dominate the picture, erosions or lesions of hemorrhagic character prevailing. Like all bullous lesions in the mouth, blisters rarely remain intact for more than a very short time, and give way to the predominant picture of a whitish-gray pseudomembranous coating, erosions or ulceration, at times, with much swelling and tenderness. Upon the lips, erosions followed by crusting develop. Involvement of the tongue is usually marked by well-defined indentations at the margins where the tongue contacts the teeth.

Under its popular-known name of Stevens-Johnson syndrome[59], this disorder, which has been variously described as, "Bullous Malignant Erythema Multiforme," "Eruptive Fever with Stomatitis and Ophthalmia"[28], "Ectodermosis Erosiva Pluriorificialis"[39], "Dermatostomatitis," and "Mucosal Respiratory Syndrome"[60], is considered by most observers to be a variant of erythema multiforme. The disease is ushered in with an acute onset with high temperature, headache, chills, malaise, sore mouth and throat and often with symptoms of upper respiratory tract infection. Vesicles appear on the lips, tongue, and buccal mucosa which soon rupture and become pseudomembranous. Soon thereafter, erosions develop which may go on to ulceration, though the process may be confined simply to an erosiveness of the parts. Salivation is profuse. The disease is often accompanied by conjunctivitis, rhinitis and balanitis. Within a few days an erythematous macular, vesicular, bullous, or petechial eruption usually appears on the hands and feet and to a lesser degree, on the trunk. The exudative lesions crust and heal in the course of from 3 to 6 weeks[28].

Another disease considered to be a variant of erythema multiforme, is Reiter's syndrome which is characterized by a triad of arthritis, urethritis and conjunctivitis. In a study of 23

cases by Hall and Finegold[34], the most frequent eruptive lesions were found in the oral cavity. These were vesicles surrounded by a zone of erythema. The vesicles soon ruptured leaving small ulcers having an erythematous areola and often coated with a thin, gray-white membrane. They were found upon the palate or buccal mucosa in 48% of the patients. Some had lesions on the tongue. Loss of papillae often gave the tongue a relief map-like appearance. These lesions are usually painless. They stated that mucocutaneous lesions were found in all patients and that the next most frequent lesions were the eruptive ones. Arthritis is a constant and distinct feature of Reiter's disease and the skin lesions mimic entirely those of keratoderma blenorrhagicum.

Behcet[7] described a disorder comprising a triad of genital ulceration, oral lesions and a wide range of inflammatory changes of the eyes, occurring in repeated attacks. This syndrome has also been variously considered as a variant of erythema multiforme. The mucous membrane lesions of the mouth consist of ulcers of the tongue and mucosa. Vesicular and ulcerative lesions appear on the genitalia, frequently with necrotic ulcers on the scrotum. The cutaneous picture comprises a variety of lesions which include those of erythema nodosum, classic erythema multiforme[48], or a papulopustular eruption.

Pemphigus. Pemphigus, a relatively rare dermatosis, usually relapsing in type, and characterized by an eruption of successive crops of bullae which develop suddenly, is a disease in which the mucous membranes of the mouth are affected sooner or later in the course of the disorder. Seldom during sustained observation does the mucous membrane escape involvement. It has been said that about 75% of the people who have been afflicted with this disease have been Jews, usually between the ages of 40 and 50 years[13]. The mucous membranes of the mouth (or the vagina) may be the primary site of involvement. According to Schraff[53], in 50% of the cases of pemphigus the oral eruption was primary; in some instances the disease has been limited to the mucous membranes. It is extremely difficult to make a diagnosis of oral pemphigus in the absence of cutaneous lesions[58]. It has always been with a feeling of apprehension that the physician awaits the development of the cutaneous eruption to verify his suspicion of the diagnosis of oral pemphigus. The development of large, painless vesicles or bullae on a normal appearing skin in patients with loss of weight, nervousness and pruritus following the rupture of the bullae and crusting of the lesions, is highly suggestive of pemphigus. The presence of Nikolsky's sign and the histological evidence of acantholysis strengthen the likelihood of pemphigus.

The oral lesions may be unrecognized because of their transitory nature and the early rupture of the bullae[13]. The first lesions to appear in the mouth are most often found on the soft palate. One or more bullae usually suddenly appear on the mucous membrane, varying in size from that of a pea or a dime to one covering the whole cheek and gums[15]. In some cases the entire oral cavity may be involved. The bullae are at first characteristically painless and because of their thinness they rupture easily. New blebs are formed. Following rupture of the blister, maceration, raw, bleeding surfaces are left, particularly hemorrhagic at the periphery of the lesions. A ragged mucous membrane remains at the edges. The denuded or eroded areas then become very painful and in some cases the sites become necrotic,

especially where large bullae had existed. This gives rise to a foul odor. Sialorrhea, according to Burket[13], is a prominent symptom. The saliva may run and drip from the mouth, frequently being blood-tinged. When cutaneous and mucosal pemphigus exists, it is said that the oral lesions produce more discomfort. It is the consensus of most observers that the prognosis is usually better when the mucosa is not affected.

Lupus Erythematosus. In recent years lupus erythematosus has received its full quota of recognition in the literature by both the dermatologists and the internists, the former having recognized the disease both in its chronic discoid form and in its acute disseminate (systemic) form for about 100 years[17]. In chronic discoid lupus erythematosus the mucous membranes of the mouth are not infrequently involved, the incidence of oral involvement ranging from 15%[13] to 28%[55] of the cases. The disorder has been known to be limited to the mouth for some time before appearing on the skin[19], but in such instances its identity has required histological confirmation. More often oral lesions coexist with cutaneous lesions, making their appearance some time after the dermal involvement has been present[13,44].

Oral lesions occur on the tongue, palate and mucosa of the cheeks and lips and the gums[37]. They may consist only of slight thickening, with duskiness and scaliness with an appearance of an abrasion of the mucous membrane[60]. Characteristic lesions[40] consist of well-defined slightly elevated, superficial patches with a dark red margin, the border of which shows numerous dilated blood vessels having a radial arrangement extending into the surrounding tissue[47]. Later the center becomes eroded or superficially ulcerated and covered with a yellowish, adherent membrane which gives way to a purplish area in which numerous whitish points or lines develop. If ulceration has occurred, the healed areas appear thinly scarred. Ormsby and Montgomery[47] have stated that periods of activity and quiescence occur, the former characterized by enlargement of the lesions by peripheral extension accompanied by the development of fresh erosions, superficial ulcerations which are then followed by atrophic changes. Extensive involvement of the mouth has been known to occur, described vividly by Finnerud[24] and Sibley[55].

On the tongue the lesions of lupus erythematosus simulate those of lichen planus or leukoplakia. Sharply circumscribed, smooth, reddish areas appear in which the papillae are lost. Occasionally erosions or superficial ulcers develop which look not unlike the erosive type of lichen planus.

When the vermilion border of the lip is involved, the lesions appear similar to those in the mouth. Small areas may be involved or the entire lip may be affected. The lips usually appear somewhat swollen, of a purplish hue and covered with adherent scale-crusts. This has often been spoken of as being suggestive of peeling collodion. The lips, as the closest counterpart of lupus erythematosus of the skin, show telangiectasis at the periphery of the patches. The lips are usually tender and sensitive, and bleeding occurs when scales are removed or when fissuring has resulted. Superficial stippled scarring often follows healing.

In acute disseminate or systemic lupus erythematosus, the lesions in the mouth are ordinarily more acute and destruction of tissue is more marked. Irregular, superficial or moderately deep ulcers develop whose edges are undermined and ragged, and covered with a necrotic, grayish-white mem-

brane. The entire picture is of a rather acute inflammatory and necrotic process, hemorrhagic in appearance, with bleeding and painfulness. There is extreme difficulty in eating.

Scleroderma. Scleroderma is a chronic disorder of apparent collagen disturbance characterized by board-like hardening and fixation of the skin which occurs in circumscribed or diffuse patches. As are visceral manifestations, involvement of the mouth is not uncommon[4,6]. Barber[4] reported a case of circumscribed scleroderma of the buccal mucous membranes in a man 43 years of age who had a white patch on the lower lip of 6 months' duration. The patch was depressed below the level of the surrounding normal mucous membrane and it extended downwards from the margin of the vermilion border of the lip to the alveolar sulcus. It was indurated and occurred as a band, narrow above and broadening out towards the lower part, and its configuration recalled the band form of the *en coup de sabre* type of scleroderma on the forehead and scalp. The conspicuous depression of the patch readily distinguished it from leukoplakia. Beerman[6] described retraction of the gingival margins with loosening of the teeth in oral scleroderma, and Stafne and Austin[57] observed an increase in the width of the peridontal spaces, seen radiographically. They stated that the posterior teeth are involved more than the anterior.

Lewy[41] observed a patient with scleroderma in whom the chief symptom was dysphagia, whereas Truelove and Whyte[64] found esophageal sclerodermatous changes with stricture formation in 3 out of 4 cases of scleroderma in which the face and neck were affected.

In scleredema adultorum, an affection which differs from scleroderma, a solid edema begins about the head and neck and sweeps downward to involve large areas of the skin. The condition usually follows some febrile disease. Frank[25] described a case of this disorder in which a man could not extend his tongue. The tongue was firmer than normal at the tip and was progressively more involved toward the posterior region. However, the palate and the uvula were affected.

Epidermolysis Bullosa. Involvement of the mouth in epidermolysis bullosa, though rare, does occur. In a disorder characterized by the development of vesicles and blisters on parts of the skin which are subject even to slight trauma, it would seem that the incidence of oral mucous membrane involvement would be much greater than the 2 to 2½% of the cases indicated by Corson[17], since the mouth is obviously subject to all sorts of trauma. In the dystrophic form of the disease, the abnormality is usually present at birth or shortly after and is characterized by more or less of a universal distribution of bullae which result in dystrophic and atrophic changes. Observers state[47,48,60] that the mucous membranes show a strikingly higher incidence of erosions, ulcerations and changes secondary to bullae in the dystrophic form than in the simple form. In the latter form, healing may lead to temporary pigmentation, but no permanent changes follow[47]. In dystrophic epidermolysis bullosa, infants may die early because of severe involvement of the mouth which trauma has provoked in nursing.

In a case presented by Corson[17], a woman of 30 years of age gave a history of marked difficulty in breast or bottle feeding when she was an infant because of blisters which would develop during the feedings. In addition to typical atrophic lesions of epidermolysis bullosa upon the legs, knuckles,

fingers and elbows, she presented atrophy of the mucosa of the tongue, cheeks and nasopharynx. She had given a history of constant development of blisters on the gums from wearing dentures and from eating rough and hard articles of food. During the course of the examination, a lima bean-sized bulla developed on the dorsum of the tongue which readily became denuded. The top of the tongue became raw from the gag which was used to effect traction on the tongue.

Oral mucous membrane involvement in epidermolysis bullosa may present bullae, infiltrated areas or leukoplakic patches anywhere within the buccal cavity[62]. Atrophy frequently follows recurrent attacks of bullae.

Acrodermatitis Enteropathica. A number of observers are of the opinion that acrodermatitis enteropathica is a disease closely related to, if not a form of, dystrophic epidermolysis bullosa[9,10,21,47]. First described by Danbolt[21], the disease has been variously described as being characterized by a vesicobullous to pustular and psoriatic eruption on the face, perineum and genitalia and extremities in children at about the time they are weaned. Additionally, they show paronychia, dystrophic nail changes, increasing alopecia to a point of almost total baldness, recurrent attacks of diarrhea and a progressive marasmus which sometimes leads to death. Dillaha *et al.*[23] described a case in which the mucosal changes of the mouth consisted of a white coating on the tongue and buccal mucosa, whereas Bloom[9], describing the disease in a 4-year-old boy, showed him to have reddish and whitish spots on the tongue and buccal mucosa, perlèche and blepharitis. The tongue was also coated with a whitish fur.

A case of acrodermatitis enteropathica in an adult was described by Piper[48]. A woman 46 years of age had had recurrent episodes of skin trouble of a seborrheic nature about the mouth and anal regions in conjunction with mucoid stools. In addition to an angular stomatitis and blepharitis, the tongue was found to be swollen, deeply furrowed, and covered with a thick, smooth, white film. She showed other cutaneous changes characteristic of the disease. Monilial organisms (*Candida albicans*) were recovered from the perlèche, paronychial lesions and from a grossly mucoid ropy stool.

Keratosis Follicularis. Frequently referred to as Darier's disease, keratosis follicularis is a disorder not often thought of as one capable of inducing lesions of the mouth. The disease is characterized by reddish, tiny, firm papules which gradually become darker and enlarge and coalesce to form papillomatous growths, frequently resulting in vegetations about the genitalia and axillae. Symmetrically distributed, the forehead, neck, shoulders and midline of the trunk are the sites most often affected. Reenstierna[50] is thought to have been the first to report mucosal involvement of the mouth in 1917, and since, there have been a few scattered reports of oral changes in keratosis follicularis. Brünauer[11] in a comprehensive review of Darier's disease, showed that the disease was capable of involving the mucous membranes and the esophagus. In one of 3 cases described by Frost[26], lesions in the mouth were present and they consisted of minute, whitish papules which gave a rough sensation to the palpating fingers. The lesions were closely set along the posterior, outer surface of the gums at the level of the bicuspids and molars and were closely set on the hard palate, becoming less frequent on the soft palate. The lips and the mucous membrane of the cheeks were not involved. Abramovitz[1] showed a

case of lesions of the hard palate and gums in Darier's disease, but they were not described. Harris and White[35] described a case of a 20-year-old woman who had red, spongy, hypertrophic gums since the advent of her permanent teeth. She had had keratosis follicularis for 5 years. At times the gums bled when the teeth were cleaned. The gums of the anterior portion of the upper jaw were so hypertrophic as to interfere with speech. There was no pain on pressure of the affected parts. The other parts of the mouth and gums were normal.

Pityriasis Rubra Pilaris. But few textbooks of dermatology mention the possible presence of mucous membrane lesions in pityriasis rubra pilaris. This disorder is a chronic, mildly inflammatory and exfoliating disease of the skin with characteristic fine, acuminate, hard papules situated at the orifices of hair follicles, frequently producing a typical nutmeg-grater effect. By coalescence, the papules form reddened, scaling areas having an appearance of a seborrheic dermatitis which may spread and cover a large surface of the body. Lesions on the mucous membranes of the mouth have been described as simulating lichen planus[27] or occurring as whitish, linseed-sized, raised papules on the palate[61]. In a case reported by Marshall[42], the whole mucous membrane of both cheeks from the angles of the mouth to the last molars and into the depths of the pouches between the gums and teeth was uniformly grayish-white and rough and had the texture and appearance of frosted glass.

Pityriasis Lichenoides et Varioliformis Acuta. Since Senear and Oliver's[54] excellent paper on pityriasis lichenoides et varioliformis acuta in 1931, this variant of parapsoriasis has become more easily recognizable and its existence found to be not entirely as rare as formerly thought. This affection, which may be considered to be a sub-variety of the guttate type of parapsoriasis, is characterized by a generalized eruption, the lesion being multiform, usually consisting of vesicular, pustular, crusted and hemorrhagic lesions which may terminate in varioliform scarring. Oral lesions have been known to occur in this disorder, but the literature discloses only 3 such reported cases. Habermann[33], whose name is often used to designate the disease, was quoted by Wise[69] as having reported a pea-sized, sharply defined superficial ulcer on the mucous surface of the upper lip. The surface was yellow, the edges clear cut and the lesion finally healed leaving a shallow depression. Ingram mentioned but did not describe a patient who had a lesion on the mucosa of the lip and and on the tongue[38]. The third case was that of Wechsler's[67]. He described a solitary lesion on the center dorsum of the tongue which consisted of a central superficial ulceration covered with a necrotic membrane and surrounded with an erythematous halo. The lesion healed without therapy in 5 days leaving a depression.

It is apparent from the meager descriptions of mucosal involvement of the mouth in pityriasis lichenoides et varioliformis acuta that the lesion of significance is a small, sharply circumscribed ulcer which terminates in a depression.

Lichen Sclerosus et Atrophicus. Over a period of years, the existence of mouth lesions in lichen sclerosus et atrophicus has been questioned. The disease as it affects the skin has a vague similarity to lichen planus but its clinical signs are so characteristic that its diagnosis becomes quite clear, not however, for the mucous membranes where oral lesions have mostly

been interpreted as lichen planus by observers, according to Miller[43]. Cutaneously, lichen sclerosus et atrophicus is characterized by an eruption which has a predilection for the neck, upper trunk, forearms, axillae, genitalia and perineal region, the lesions consisting of ivory white, polygonal, flat-topped, firm papules which coalesce to produce patches. The papules show tiny follicular depressions and horny plugs, and when atrophy occurs characteristically in later stages, the plugs and depressions become more conspicuous. Eventually, diffuse parchment-like atrophy develops, with wrinkling and depigmentation[47]. The disease most often affects women.

In a case of lichen sclerosus et atrophicus described by Hoffman[36] and quoted by Miller[43], lesions in the mouth consisted of a coin-sized, nonindurated, slightly reddish area with delicate stripes on the mucous membrane of the left cheek and similar changes were present on the surface and margins of the tongue. This was acceptable as lichen sclerosus et atrophicus, but no histopathological proof was established. In Miller's case[43], in a woman aged 48, oral lesions were found 7 months after initial examination, about 2½ years after the onset of the cutaneous eruption. The findings in the mouth revealed a well-demarcated grayish-white area on the inner surface of the left cheek, about 2 cm. in diameter. The area was smooth and soft and composed of delicate coalescent papules without surrounding reaction. A similar, but smaller, partially erythematous area was present on the right cheek. No subjective symptoms accompanied the eruption in the mouth. Histopathological examination of a biopsy of an oral lesion confirmed the diagnosis of lichen sclerosus et atrophicus. This appears to be the first case of the disease with oral lesions histopathologically confirmed.

Ravits and Welsh[49] wrote of case reports of unusual lichen sclerosus et atrophicus involving the buccal mucosa. One case was believed to be the first reported of the disease with mouth lesions only, while the other 2 cases had mouth lesions in addition to lesions on the body. They stated that the primary lesion in the mouth is similar to that seen on the skin, namely, a small white papule. The papules remain discrete or coalesce to form well-defined plaques showing central delling. The papules are slightly raised and a superficial infiltration can be palpated. In the course of involution, the white surface becomes atrophic and wrinkled in appearance. In the case in which the disease was limited to the mouth, a 24-year-old man showed a grayish-white atrophic patch on the right upper cheek extending from the commissure of the mouth to the anterior pillars and gingival margin. Additionally, there were a few small, white atrophic areas on the hard palate. Biopsy of the affected mucosa showed changes compatible with lichen sclerosus et atrophicus. Buccal findings in the second case showed white papules with central delling, some which coalesced to form plaques on the palate, anterior pillars and the cheeks. In the third case, also one in which cutaneous lesions were present, grouped white papules, elevated and delled, were present on the buccal mucosa of the right cheek.

The recent reports of 4 cases of lichen sclerosus et atrophicus involving the mouth seem to indicate that such involvement is not as rare as had been generally thought.

Urticaria Pigmentosa. The characteristics that distinguish urticaria pigmentosa have broadened considerably since its description almost 90 years ago.

Originally it was described by Nettleship as a chronic eruption of yellowish or brownish pigmented lesions which urticate (dermographism) upon mechanical rubbing, its onset occurring in early infancy as macules, papules or nodules. Later, the concept broadened to include bullous and telangiectatic forms and with the possible development of the disease in adults, as well. Histopathologically, a mast cell infiltration is found in most cases.

Once thought to be a disease confined to the skin, urticaria pigmentosa, by an ever-increasing number of observations, indicates that it may affect other organs and may involve any area of the skin or mucous membrane. Though there have been many reports revealing systemic involvement, with an abnormal increase in mast cells in various tissues and organs of the body[22], yet descriptions of invasion of the mouth have been most meager. Berlin, in a paper on urticaria pigmentosa as a systemic disease[8], gives what appears to be the first detailed description of involvement of the mouth in an old man. The mucous membranes were very pale. Small isolated grayish macules were seen on the tongue and palate. Eight months later the visible mucous membranes had become severely involved, showing matchhead-sized round, depigmented papules on the internal and external lips, the gums, the dorsal surface of the middle and posterior thirds of the tongue, on the soft and hard palate and on the pharynx. Though not describing nodules, the legend on a photograph of the tongue told of "multiple nodular lesions" on the posterior part.

It is the feeling of this writer that more cases of mucous membrane involvement in urticaria pigmentosa will be brought to light, especially in the systemic forms, generally seen in adults who would be more apt to complain of symptoms in the mouth.

Acanthosis Nigricans. Acanthosis nigricans is a disorder which often shows an oral counterpart of the eruption that is present on the skin. The disease is distinguished by a papillomatous hypertrophy and hyperpigmentation which has a predilection for the creased areas and folds of the body. Curth[20] has divided cases into 2 classes, one of which is referred to as the "benign type" in which the papillary changes remain more or less stationary and in which the general health is usually unaffected. In the other, referred to as the "malignant type," it is most often associated with a usually-fatal type of internal carcinoma. In the mouth, painful sensations may exist, and papillary infiltrations resembling acuminate warts have been noted. Condylomatous growths have also been described on the surface of the tongue according to Ormsby and Montgomery[47].

Grace and Schwartz[29a] have stated that in 50% of the cases of acanthosis nigricans oral pigmentation exists. They described a case of a 46-year-old woman whose disease began in the mouth and was followed later by typical changes in the skin. A detailed description of the oral picture disclosed a dull red area covering the uvula, the anterior pillars of the fauces and adjacent portion of the buccal mucosa. Dilated blood vessels appeared on the surface of this area. The hard and soft palates and gums were studded with innumerable pinhead-sized papules and there was a raised, fissured, smooth plaque of mucosa extending from a point 3 cm. behind either angle of the mouth and crossing the midline on the buccal aspect of both lips. These plaques were soft and elevated. The tongue was enlarged

red and devoid of fur and was fissured on the anterior half. The papillae were especially prominent over the entire surface of the tongue.

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DERMATOLOGY AND SYPHILOLOGY

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THE PORPHYRIAS: A DISCUSSION OF SOME CURRENT CONCEPTS

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IN recent years there have been many articles discussing the importance of pigment metabolism and disease. Diseases involving the so-called respiratory pigments, especially the porphyrins, have received much attention by the dermatologist because of the photosensitive cutaneous manifestations, the neuropsychiatrist because of grave mental and neurological signs, and the surgeon because of the curious abdominal symptoms. They have become interested and have contributed to the basic understanding of this group of diseases. The voluminous literature needs consolidation. This paper attempts to correlate from the recent literature what, in our opinion, are contributions to the practical aspects of this problem.

This is in no sense a monographic presentation. For extended details and discussion of various aspects of the problem, the reader is referred to the works of Brunsting, Watson and his group; Zeligman; Dobriner and Rhoads; Markovitz; Barnes and his co-workers; Shemin and Russell, and Waldenström.

DEFINITION. Porphyria designates a group of diseases with abnormal porphyrin metabolism characterized by an increase in urinary excretion of uroporphyrin or its precursor porphobilinogen. The porphyrias must be differentiated from porphyrinuria, which is simply an increase in urinary coproporphyrin

and not in uroporphyrin.* Porphyrinuria accompanies and may be symptomatic of many diseased states, namely, febrile disorders, severe anemias, heavy metal intoxication, cirrhosis of the liver[54], infectious hepatitis, infectious mononucleosis, in cases of mechanical jaundice[51], acute pancreatitis, and some malignancies[58]. In spite of the general importance of the processes associated with porphyrinuria, no characteristic dermatoses occur with it.

BIOCHEMISTRY. The biochemistry of porphyrin metabolism was originally described by Hans Fischer in 1915. He isolated a dark red-brown pigment from the urine of a patient suffering from what is now considered as erythropoietic porphyria. He called this pigment uroporphyrin[12]. A second red-brown pigment which was present in both urine and feces he named coproporphyrin[11].

Porphyrins are cyclic compounds formed by the linkage of four pyrrole rings through methylene bridges and related structurally to a parent compound which Fischer called porphin[13]. A characteristic property of the porphyrins is the formation of complexes with metal ions in which the metal ion is bound to the nitrogen atom of the pyrrole rings. Examples are the iron porphyrins such as heme of hemoglobin and the magnesium-containing porphyrin chlorophyll, the photosynthetic pigment of plants.

In nature, the metalloporphyrins are conjugated to proteins to form a number of compounds of importance in biological processes. These include hemoglobin, myoglobin, cytochromes, and catalases. Rimington[31] suggests that the porphyrin nucleus serves to enhance the chemical activities of the metallic ion with which it is united.

Recent studies indicate that the porphyrins are synthesized in cells from two starting compounds, "active succinate," the Coenzyme A derivative of succinic acid, and the amino acid, glycine. These two compounds combine to form alpha amino-B-keto-adipic acid, which undergoes decarboxylation to produce delta aminolevulinic acid[42]. It is then postulated that two molecules of delta aminolevulinic acid condense to form the first pyrrole, porphobilinogen[26,38,41,43,57]. Porphobilinogen may then lose a methyl amine residue, and, by a condensation of four of the resulting monopyrroles, the hypothetical first tetrapyrrole, uroporphyrin, would be formed[7,25,50,56].

The porphyrins found in nature are compounds in which various side chains are substituted for the 8 hydrogen atoms. As a simple means of showing these substitutions, Fischer proposed a shorthand formula in which the methylene bridges are omitted and each pyrrole ring is shown as a bracket with the 8 substituent positions numbered.

The arrangements of the substituents may be asymmetrical or symmetrical. If the substituent is asymmetrical, the porphyrin is classified as Type III. A porphyrin with a completely symmetrical arrangement of the substituents is classified as a Type I porphyrin. Only Types I and III are found in nature, and the Type III series is by far the more abundant.

Because of the presence of tertiary nitrogens in the two pyrrole rings contained in each porphyrin, these compounds act as weak bases. Those which possess a carboxyl group on the side chain act also as acids. As a result, such compounds are weakly amphoteric. Their isoelectric points range from pH 3.0 to 4.5, and within this pH range the porphyrins may easily be

*The normal value for coproporphyrin excretion in the urine ranges from 60 to 280 micrograms per day.

precipitated from an aqueous solution.

The various porphyrins are all colored. In the study of porphyrins or porphyrin derivatives, the characteristic absorption spectrum which each exhibits, both in the visible and the ultraviolet regions of the spectrum, is of great value. Hematoporphyrin, for instance, has a sharp absorption band near 400 mu. This is a distinguishing feature of the porphin ring and is characteristic of all porphyrins regardless of the side chains present. This band is termed the Soret band, after its discoverer. Hematoporphyrin in acid solution, in addition to the Soret band, has two weaker absorption bands with maxima at 550 and 592 mu.

In organic solvents, porphyrins have four main bands in the visible spectrum as well as the Soret band. For example, a solution of protoporphyrin in an ether-acetic acid mixture exhibits absorption bands at 632.5, 576, 537, 502 and 395 mu. When porphyrins dissolved in strong mineral acids or in organic solvents are illuminated by ultraviolet light, they emit a strong red fluorescence. This fluorescence is so characteristic that it is frequently used to detect small amounts of free porphyrins. The double bonds in the porphyrins are responsible for the characteristic absorption and fluorescence of these compounds, and the reduction (by addition of hydrogen) of the methene (C=H) bridges to CH_2 leads to the formation of colorless compounds termed porphyrinogens.

The presence of coproporphyrins or of uroporphyrins is of clinical interest since these two types of compounds are excreted in increased amounts in the porphyrias. They also are considered as endogenous photodynamic agents capable of producing a spectrum of visible cutaneous reactions[45]. Coproporphyrins I and III are soluble in glacial acetic acid-ether mixtures, from which they may then be extracted by hydrochloric acid. Uroporphyrins, on the other hand, are not soluble in acetic acid-ether mixtures but are partially soluble in ethyl acetate, from which they may be extracted by hydrochloric acid. In the HCl solution ultraviolet illumination gives a characteristic red fluorescence. A spectrophotometer may then be used to demonstrate the characteristic absorption bands. The melting point of the methyl esters of the various porphyrins may also be used to differentiate them[10,52]. Paper chromatography has recently been employed as a means to separate and identify the porphyrins[19].

CLINICAL TYPES OF PORPHYRIA. The most practical classification of porphyria proposed is that by Schmid, Schwartz and Watson[36]. This is based on their concept of the site of origin of the porphyrin of abnormal quantity and type found in the urine[49].

1. Porphyria erythropoietica, indicating that porphyrins are found in large amounts in the bone marrow.

2. Porphyria hepatica, which suggests the liver as the site of formation of abnormal types and increased amounts of porphyrins. This is further subdivided into (a) acute intermittent porphyria, (b) porphyria cutanea tarda, and (c) mixed type.

Erythropoietic Porphyria. (Congenital porphyria). This rare type of porphyria occurs during infancy or early childhood, and is transmitted as a single recessive gene with partial sex limitation to males. Consanguineous marriages are frequent in affected pedigrees. In very rare instances a dominant mode of inheritance is evident[28]. It is characterized by pink or reddish urine and a blistering eruption of the skin when it is first exposed to light. Crops of bullae appear on the face, ears, and uncovered portions of the skin of the hands and arms; sun-

light, heat and trauma are precipitating factors. In time the bullae increase in intensity, the denuded skin becomes infected and extensive scarring and mutilation occur. The corneas are sometimes involved. The deciduous teeth are stained brown or brownish red and the bones are also impregnated with porphyrins. Melanosis and hypertrichosis occur. A hemolytic process is nearly always present in these patients which has led to the postulate that excessive generation of Type I porphyrins reflects abnormally rapid hemoglobin synthesis stimulated by hemolysis[1,16,17,20,24,32,34,35]. Splenomegaly, hemolytic anemia and osteoporosis are serious later complications.

Of interest to the dermatologist is the cutaneous appearance under ultraviolet light of one patient with erythropoietic porphyria as described by Cornbleet[8]. This patient, a young girl, showed patches of a deep purplish hue at areas usually exposed to light, such as the face and hands. These changes appeared at sites of apparently normal skin, as well as hyperpigmented parts. Frozen sections of biopsy specimens from these activated places fluoresced a greenish-blue at the epidermis under the fluorescence microscope.

Acute Intermittent Porphyria. There is evidence that acute intermittent porphyria is often transmitted as a dominant trait of variable expressivity[4]. Possessors of the gene may be asymptomatic, exhibiting only abnormal porphyrins in the urine. Relatives of obviously affected persons should be routinely examined for the presence of abnormal porphyrins in the urine[21]. Photosensitivity is absent. This disease is more common in adult women. Although rare, it is somewhat more common than congenital porphyria, and is characterized by episodes of intermittent acute abdominal, neurologic, or mental symptoms followed by asymptomatic periods. The demonstration of porphobilinogen is diagnostic of this type of porphyria. Uroporphyrin of Type I is excreted in the urine.

The disease has been traced through 2 or 3 generations. Cases have been reported in the same family[23]. The recognition of such cases is of practical importance, because acute attacks have been precipitated in porphyria patients and in their unsuspecting relatives by such drugs as barbiturates[33].

Nervous system disturbances are common and may be the first manifestation of an attack, although they often occur as the abdominal symptoms are subsiding. Frequently, bizarre complaints without objective findings lead to a diagnosis of neurosis or hysteria. The development of neurologic symptoms is of grave significance, and may increase the immediate mortality rate to as high as from 50 to 75%.

In a review of 69 patients with acute intermittent porphyria by Markovitz[21], gastrointestinal symptoms, peripheral neuropathy, mental or psychic changes, cranial nerve involvement, and vital signs were of significant diagnostic importance. As far as gastrointestinal symptoms were concerned, severe colicky abdominal pain was the major symptom. This pain may mimic that seen in any acute surgical emergency and may last hours to months. Characteristically, the physical findings do not support the diagnosis of a surgical emergency. The patients may complain of tenderness on palpation, but there is no rebound tenderness, and the abdomen is soft.

In this series of 69 patients, 32 had been operated upon a total of 48 times, with appendectomy or laparotomy accounting for almost 80% of these. There were several instances of cholecystectomy and of unilateral nephrectomy. The great majority of the operations

would not have been performed had the correct diagnosis been made. The significance of this to the surgeon is stressed.

Nausea or vomiting or both accompanied the abdominal pain in 36 of the patients, and constipation was specifically mentioned in 32. Waldentroöm[46] thought constipation was probably always present, but he also noted 8 patients who had diarrhea. In the 69 patients reviewed here, only 8 had diarrhea, or diarrhea alternating with constipation.

Concerning peripheral neuropathy motor symptoms which varied from weakness to tetraplegia were reported in over 75% of the patients. The weakness may begin anywhere, and it progresses unpredictably. The older literature speaks of Landry's ascending paralysis as being a characteristic finding. This was first denied by Waldenström, and in this series was noted only six times. Several references point to the almost functional appearance of the weakness as though the patients could overcome it if they tried.

In 39 patients of this series, the deep tendon reflexes were lost or hypoactive. They could be present one day and absent the next, only to reappear later. The variability of the deep tendon reflexes has been stressed. It has also been noted that the quadriceps reflex might be absent while the Achilles reflex was brisk. Similar bizarre reflex change was noted in 15 instances. The weakness and deep tendon reflex changes may persist for prolonged periods and still be followed by complete recovery.

Sensation has previously been reported as being intact, but in this series minor sensory loss, usually limited to diminished perception of pinprick, was described in 17 patients. The sensory examination was, however, very difficult to evaluate because of the severe muscle pain and tenderness on palpation noted in 55% of patients. The muscular pain was often described as burning or aching in character and was occasionally the chief complaint.

Mental or psychic changes were present in over three-fourths of the patients reported in this series. Minor changes such as irritability, tiredness or restlessness occurred in 28 patients. In 36 instances hallucinations, delirium, confusion or epileptiform seizures were noted. In 18 patients a diagnosis of hysteria, schizophrenia, depression or paranoia was made.

Thirty-five of the patients had cranial nerve involvement which varied from mild vocal cord paresis to respiratory failure and death. There was no report of cranial nerve involvement without peripheral nerve involvement. In the entire series, vocal changes of some type were noted in 26 patients.

Thirty-four patients exhibited hypertension of 150/100 mm. Hg or above, and an equal number had tachycardia. Since, in many instances, the blood pressure and pulse rate were not recorded during the acute phase of the disease, it is probable that hypertension and tachycardia occurred even more frequently.

Fever, almost always low grade, was noted in over one-third of the patients at some point in the course of the disease. In many instances this may have been due to secondary infection. Many case reports specifically denied the presence of fever during the early acute phases of the disease.

It is apparent that the clinical features of acute intermittent porphyria may be protean; nevertheless, the natural history of the disease becomes evident in most instances although the diagnosis at any one time may be difficult[29]. Fischer (Illinois Med. J., 111, 313, 1957) has shown that acute porphyria is in reality a chronic process

characterized by exacerbations and remissions over a long period of time, months to years.

Three cases with concomitant diabetes mellitus and porphyria are recorded by Sterling, Silver, and Ricketts[44]. In each instance, diabetes preceded the onset of symptoms of porphyria. They suggest that glucose tolerance tests be performed in cases of porphyria and that urinary porphyrins be sought in cases of diabetes, especially those in which the condition is thought to be "diabetic polyneuritis."

Porphyria Cutanea Tarda. In porphyria cutanea tarda, that is, the purely cutaneous type, the onset is at middle age or later. The course is mild but persistent and is more common in males than females. The familial trait, a mendelian dominant, is shown in some cases. Hepatotoxic factors are prominent, and functional impairment of the liver is common. Porphobilinogen is absent. In practically all cases the skin disease is the major complaint[5]. Hypertension is common but no evidence of hemolytic disease is found. Characteristically, there is a low grade blistering and erosive tendency of the light-exposed surface of the skin, with melanosis, hypertrichosis and violaceous hue. The hyperpigmentation may be a diffuse or mottled process. Sclerodermoid yellowing and hardening of the exposed skin of the face and back of the neck is common. Occasionally, punched out craters and healed scars are observed about the cheeks and back of the neck. Blistering is an irregular feature, occurring mostly on the fingers and hands.

Recently Waldenström[47] has suggested that there is more than one type of porphyria cutanea tarda. He suggests two major divisions: porphyria cutanea tarda symptomatica and porphyria cutanea tarda hereditaria. In the symptomatic type the abnormal porphyrin excretion is secondary to liver damage, the most common being chronic alcoholism and the more rare type liver cell adenoma. He considers that these types are not true porphyrias. Although porphyria cutanea tarda hereditaria has not as yet been clearly defined, Waldenström suggests that this type is inherited as a dominant trait and would classify this as a true porphyria.

Dean and Barnes[9], and Scott and Grotepass[40] have shown that in South Africa typical porphyria cutanea tarda is relatively common in some Bantu populations. Although nutritional cirrhosis of the liver is also common in South Africa, alcoholism apparently plays no important part in the background of this process[2]. Excessive radiation from the sun plus liver damage may explain these cases[9]. Barnes, Frootko and Parnell[3] presented a patient with porphyria cutanea tarda which resembled clinically the congenital form of the disease, but full investigation has shown that most probably he was a familial hepatic porphyric. The early onset (age 6 months) is an exception to previous experience of this disease in South Africa.

Mixed Type. Age of onset is younger in this than in the porphyria cutanea tarda group as a whole. The blistering skin reaction is often explosive and directly related to exposure to the sun. Attacks of abdominal or nervous symptoms coincide or alternate with the cutaneous phase or smolder intermittently in the background. Here, too, a familial factor is not uncommon. Porphobilinogen may be found in the freshly voided urine[48].

HISTOPATHOLOGY. The histopathologic changes of the cutaneous lesions of porphyria are not distinctive. The bullae are of the tension type without acantholysis. In the acute vesicular photosensitive reaction, the base of the

bulla shows a focal necrotic reaction about the smaller blood vessels of the cutis[27].

Brunsting[5], who studied many biopsy specimens from 10 patients with porphyria cutanea tarda, gives a detailed description of the histopathological findings. He noted that the microscopic examination revealed that the bulla was usually of the subepidermal type as a consequence of tension or pressure. The overlying keratin layer was thickened and showed parakeratosis. Cellular material in the bulla was scarce; acantholysis was not seen. In four specimens, at the base of the bulla, villiform projections of dermal papillae, containing dilated capillaries, were seen to rise irregularly from the floor in a festooned arrangement. The upper part of the cutis showed a moderate, inflammatory reaction. The elastic and collagen fibers were merged to give the characteristic tinctorial reaction of senile skin. In some instances the walls of the blood vessels showed hyaline thickening.

Microscopic examination of specimens of sclerodermoid skin showed increased melanosis as a rule; amorphous deposits occurred in the cutis; irregularly outlined, staining bluish with hematoxylin and eosin, and staining yellow with van Gieson's stain. In the centers of these masses, collagen and elastic fibers were disorganized and merged so as to be indistinguishable. Special elastic tissue stains showed fragmentation and tangling of the elastic tissue into purplish clumps at the borders and beneath the homogeneous zones. Stains for amyloid were negative. This is the picture of the change in skin after chronic light exposure, including the so-called senile skin.

A positive periodic acid-Schiff reaction was seen in certain sections of tissue, in the granular layer and midzone of the epidermis, in the amorphous masses in the cutis, and, to some extent, in the thickening hyalin-like walls of the deeper capillaries, but deposits of glycogen were not outstanding. Similar staining reactions have been reported recently in specimens of skin subjected to traumatic irritation with adhesive tape. The deposits of glycogen, then, are probably a response to an irritant of indefinite character. Apparently, none of the microscopic changes observed here in the skin are specific for porphyria.

Examination of 10 unstained specimens (embedded in paraffin and also those deparaffinized) under the fluorescent microscope, using a 100-watt light source through a Corning filter, No. 5153, showed no evidence of fluorescent material. These negative results may have been due to inadequate light source, the loss of porphyrins in the preliminary fixing process, or the absence of fluorescent material in the first place. Further studies are in progress. No porphyrins were demonstrable in the analysis of the blister fluid.

Others have demonstrated a blistering and edematous reaction of the hand in a man with porphyria cutanea tarda after exposure to natural sun through windowglass (above 3,200 A.), and by exposure to a carbon arc light source (3,500 to 4,100 A.). These coincide well with the range of the absorption bands of the porphyrins (around 4,000 A.). The patient's serum was fluorescent and contained protoporphyrin. This is the first valid demonstration of photosensitivity in cutaneous porphyria. So far, it has not been possible to confirm this effect in the lower-grade cutaneous reaction observed in the patients of this present series.

The mechanism of the photosensitive reaction in porphyria is not clearly understood. Blistering on exposure to the sunlight does not generally occur

in the commonest forms of the disease, the intermittent acute type, although more or less pigmentation is the rule. It is assumed that the photosensitive reaction in porphyria erythropoietica and in porphyria cutanea tarda is related to the presence of the highly sensitizing uroporphyrin I. In the acute types, the porphyrins are present chiefly in the form of precursors. With the newer technical methods which utilize microassay and fluorescent microscopy, this question may soon be solved.

The pathological changes in the nervous system were recently reviewed by Schwarz and Moulton[39]. In their study of 47 cases, several patterns were suggested. In the first place, there seem to be some cases in which the pathologic process effects only or chiefly the peripheral nerves. There may be slight changes in the anterior horn cells in such cases, secondary to peripheral nerve involvement. The pathologic changes described in the peripheral nerves are in no way pathognomonic of porphyria, being chiefly a patchy asymmetric Wallerian type of degeneration. Some changes have been believed to resemble those produced experimentally by ischemia. Infiltrating cells and pigment have been noted in the demyelinated peripheral nerves. The Schwann cells and the connective tissue elements have shown proliferative responses at times. Of the 47 reports, the peripheral nerves were examined in 25 cases and in only 5 were they found to present no abnormality. Apparently, therefore, the peripheral nerves are quite vulnerable in porphyria and react to give the histopathologic picture seen in any toxic multiple neuritis.

The next pathologic pattern that seemed apparent from a study of the literature was the involvement of the neurones of the neuraxis. Of the 47 cases, the spinal cord was examined in 41. In 10 of them, no alterations were seen in the spinal gray or white matter. Indeed, in only 5 cases was there evidence of damage to the white matter of the spinal cord, but in 31 cases definite changes were noted in the neurones of the spinal cord. The neurones chiefly involved were the anterior horn cells. Occasionally, the neurones in Clarke's column, in the lateral horns, or in the posterior horns were reported to show changes. While the disease process was often noted diffusely throughout the cord, it was not unusual to have reported greater involvement at the lumbosacral or cervical levels. The neuronal changes occurring in the spinal cord were, again, not pathognomonic of porphyria; there were cytoplasmic pigmentation, cell sclerosis, severe neuronal disease, vacuolization and cell loss, but chiefly swelling of neurones and chromatolysis. Some authors believed that the anterior horn cell changes were secondary to the peripheral nerve changes.

The brain stem was examined in 17 cases. In none was there definite changes in the white matter, while in 10 cases there were variable changes in the neurones of the somatomotor and visceromotor nuclei of the brain stem. The neuronal changes were essentially like those noted in the spinal cord but were usually less severe. Some variable vascular changes were reported in a few cases, but these findings were not consistent or marked.

The cerebellum was studied in 17 cases, with changes noted in 10. In these cases, the neurones of Purkinje or of the dentate nucleus, or both, were damaged.

The cerebrum was investigated in 27 cases. Significant changes were noted in 20 of these. The changes consisted of neuronal disease of varying types and degree in various cortical

areas. Again, there was nothing to be considered here as peculiar to porphyria.

Throughout the spinal cord, brain stem, cerebellum, and cerebral hemispheres it would seem that porphyria chiefly affects neurones, most profoundly in the spinal cord but somewhat throughout the entire central nervous system. This is the picture encountered in a polioencephalomyelitis.

Of interest were the destructive changes noted in the spinal ganglia and in the autonomic ganglia. The former, along with the peripheral nerve changes, might well explain some of the pain, paraesthesias, and other sensory disturbances encountered in these cases. In one case, the writers noted changes in the neurones of the nucleus ventralis posterolateralis of the thalamus, which would indicate further sources of sensory disturbances in such patients. The involvement of the autonomic ganglia has been suggested as possibly one of the sources of the abdominal pain which dominates the early clinical events in porphyria. This, too, may explain the various other gastrointestinal and visceral symptoms so often noted in porphyric patients.

The neuropathologic finding in one case indicated involvement of the following structures throughout the nervous system: the leptomeninx (pia arachnoid), the intrinsic vascular system, and the neurones. The meningeal involvement was chiefly over the cerebral hemispheres. It consisted of swelling of the pia arachnoid and an infiltration with red blood cells, lymphocytes, monocytes, and particularly, plasma cells. The vascular system within the neuraxis showed the most marked changes in the brain stem and the least in the spinal cord. These changes were edematous, proliferative, and exudative. The most conspicuous and consistent vascular finding was the perivascular accumulation of plasma cells and lymphocytes. Possibly of more significance was the tremendous damage to the nerve cells. The neuronal changes were nonspecific cellular changes: edematous cell change, severe acute neuronal disease, chromatolysis, cell sclerosis, and, especially, the so-called ischemic-homogenous cell disease. The distribution of the lesions could not be considered as characteristic, the anterior horn cells, especially in the cervical portion of the spinal cord; various nuclei of the brain stem; the dentate nucleus of the cerebellum; the large neurones of part of the putamen and of the globus pallidus; the neurones of certain thalamic nuclei; the giant cells of Betz in the motor area of the cortex, and the neurones in the autonomic ganglia. The glia seemed to participate only in a passive way. The myelinated fibers showed insignificant alteration. There seemed to be little evidence in this study to relate the vascular with the neuronal changes, although here and there this was suggested. The total neuropathologic picture suggested a toxic, rather than a metabolic, effect.

The neuropathologic findings in another case also showed absence of change in the myelinated structures of the neuraxis and spinal roots. Essentially, pathologic changes involved the leptomeninx and neurones. The vascular effects were pigmentation of blood vessel walls and perivascular hemorrhages. The cerebral subarachnoid space disclosed a picayune hemorrhage. The neurones of the cerebral cortex were particularly changed, suggesting an acute toxic ganglion cell disease. There was less change noted in the neurones of the spinal cord. If survival of the patient had been longer, possibly more extensive neuropathologic effects would have occurred.

PROGNOSIS. Although the porphyrias are related, they differ widely as concerns their clinical course and ultimate prognosis. As indicated below, each type varies not only with its primary metabolic error but also with the major clinical complaint and associated abnormalities.

Porphyria Erythropoietica. Aside from complications (hemolytic anemia) and disfiguring mutilation, prognosis is good.

Acute Intermittent Porphyria. In acute intermittent porphyria, mortality and morbidity have been high. The gastrointestinal disability alone has prevented patients from being self-supporting since the sequelae of one exacerbation persists as the next exacerbation begins. Frequently patients with initial symptoms limited to the gastrointestinal tract later exhibit neurological symptoms. When neurologic symptoms appear, the mortality approaches 90% in a single attack. If symptoms remain limited to the gastrointestinal tract, the mortality is said to be 20%[30].

Porphyria Cutanea Tarda. The skin lesions of porphyria cutanea tarda are generally mild but persistent. The clinical picture remains the same over a period of years, while large amounts of porphyrins are drained through the excreta. The prognosis, therefore, is favorable, especially when all hepatotoxic factors are eliminated and attention paid to any associated abnormalities.

Mixed Type. The prognosis in the mixed type varies directly as to the preponderance of symptoms and signs of the acute intermittent variety. The more prominent the symptoms of the acute intermittent variety, the more serious is the prognosis.

LABORATORY FINDINGS. The major chemical abnormality in any of the porphyrias and that which is diagnostic of them is the finding of increased urinary excretion of uroporphyrin or its precursor porphobilinogen. It must be understood and as indicated below that porphobilinogen is diagnostic of and limited to the acute intermittent variety or the mixed variety, or both. Porphobilinogen is not found in the other types of porphyria, namely, erythropoietica porphyria or porphyria cutanea tarda.

Porphyria Erythropoietica. Anemia may be significant in cases of porphyria erythropoietica. It has been stated that all cases of porphyria congenita eventually develop hemolytic anemia. Hence, all suspected cases should be evaluated with this point in mind: reticulocyte counts, serum bilirubin, fecal urobilinogen, bone marrow aspiration, fragility tests, Coombs test, cold agglutinins and hemolysins, and others. Urine color may be helpful. The color may be pink, red or black. The urine darkens on exposure to light. The porphyrin is excreted in the free form and 5 absorption bands may be seen spectroscopically, including one in the lower red region of the spectrum. Fecal coloration is not helpful unless the porphyrin content is markedly elevated; then a dark reddish brown may be noted. Oxidation eventually leads to the appearance of a black stool. Urine porphobilinogen is always negative. Liver function studies have been reported as being normal. Liver biopsy has been found to reveal normal tissue. The urine contains large amounts of uro- and smaller amounts of coproporphyrin I, while the reverse is found in the feces[53]. Fluorescence microscopy of erythrocytes and bone marrow demonstrate a marked reddish glow which is particularly prominent in the marrow. Porphyrin assay of erythrocyte and bone marrow reveals elevated uroporphyrin, coproporphyrin, and protoporphyrin levels.

Acute Intermittent Porphyria. There

is no evidence of hemolytic anemia in patients with acute intermittent porphyria. The urine may be burgundy in color or become so on standing. A normal colored urine does not exclude the presence of acute intermittent porphyria. The urine fluoresces a reddish color when placed under ultraviolet light. Urine porphobilinogen is positive during an attack. It may be positive in remission. Family members with so-called latent porphyria may have a positive test for this chromogen. It is to be noted that there is no correlation between the degree of positivity of the test and symptomatology. Liver tests reveal evidence of definite impairment. Liver biopsy is essentially normal. Bone marrow elements are within normal limits. Porphyrin levels in excreta; Waldenström zinc complex (uroporphyrin I and III plus zinc) and coproporphyrin III are elevated. Blood serum and plasma may contain significant amounts of uroporphyrin. Bone marrow porphyrins are normal. Porphyrin assay of liver sample reveals large amounts of porphyrin precursor or chromogen (including porphobilinogen) most of which appears after heating. Study of liver material secured at necropsy reveals large amounts of porphobilinogen and zinc uroporphyrin I.

Porphyria Cutanea Tarda. In patients with porphyria cutanea tarda, liver biopsy may reveal normal tissue, fatty metamorphosis, or frank cirrhosis. Liver tests reveal hepatic impairment. Fluorescence microscopy of a liver sample in the cutanea tarda group reveals an intense fluorescence in the polygonal cells. The reddish glow lasts 15 minutes under ultraviolet light, which feature is characteristic of the uroporphyrins. Liver porphyrin assay (uroporphyrin, coproporphyrin, and protoporphyrin) shows elevated levels of these substances. Heating liver tissue may decrease the amount of the uroporphyrin. Large amounts of preformed uroporphyrins in the liver are characteristic of the cutanea tarda group. No precursors or chromogens are found. Uroporphyrin III and I are found excreted in the urine and feces.

Mixed Type. The laboratory findings in the mixed type of porphyria vary with the major symptom complex presented at the time of study. Since this form is a mixture of the acute intermittent porphyria and the porphyria cutanea tarda types, the laboratory findings may be a mixture representative of either or both types.

TREATMENT. *Porphyria Erythropoietica.* Since porphyria erythropoietica is a photosensitive form, patients with this type must be protected from the rays of the sun. Recently, splenectomy has been performed successfully in a few cases. This has resulted in a diminished porphyrin excretion and disappearance or improvement of photosensitization and also in a decrease in hemolysis[18].

Acute Intermittent Porphyria. Many forms of therapy have been tried in patients with acute intermittent porphyria. Many of the drugs employed are: liver extract, ganglionic blocking agents[35], folic acid[6], vitamins, B.A.L.[37], neostigmine[14], and the steroids[15]. None of these have been conclusively successful. In an interesting recent article by Monaco and his colleagues[22], it was demonstrated that chlorpromazine was successful in controlling symptoms of acute intermittent porphyria in 4 patients. They found that nervous and abdominal symptoms were consistently relieved with the use of this drug. Initial doses of 25 to 50 mg. parenterally or orally were effective in controlling symptoms or aborting first or early attacks. Subsequent attacks sometimes required larger doses, up to 100 mg. four times each day, with somewhat less

prompt relief. Barbiturates and alcohol must be avoided, especially during an attack. These precautions must be observed in dealing with family members manifesting latent porphyria. In the event of respiratory paralysis, a respirator may tide the patient over.

Porphyria Cutanea Tarda. With the diagnosis of porphyria cutanea tarda, it is essential that the liver status be improved and protected. It is imperative that the use of alcohol be avoided and a well-balanced diet be prescribed. Patients must avoid the sun's rays, especially during the spring and summer months, during which time a sun screen preparation would be useful.

Mixed Type. Since the mixed type of porphyria has features of both the acute intermittent variety and the cutaneous tarda group, therapy must be directed at improving the liver status as well as avoiding the rays of the sun. For any acute manifestations, chlorpromazine should be tried.

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PROCEEDINGS OF

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Seminar on Cholesterol Metabolism

Dietary Fats and Serum Lipid Levels. J. C. Carson, M.D., P.T. Kuo, M.D., and C. F. Kay, M.D. (Department of Medicine, University of Pennsylvania). It is a matter of debate as to whether the amount and type of dietary fat influences the blood lipid levels. In order to investigate the relationship of dietary fats and blood lipids a series of patients has been followed for periods of several months to over 4 years.

Eight patients with elevated blood lipids and evidence of coronary and peripheral arteriosclerosis were maintained on a 20 gm. fat diet over 8- to 52-month periods. There were significant decrements in cholesterol, fatty acid, and phospholipid levels. On this diet these patients had an initial weight loss of 11 to 21 pounds, depending roughly on the previous level of obesity.

One patient showed rapid changes in his blood lipids proportional to his fat intake without any significant change in body weight over a 14-month span.

The unsaturated vegetable fat, Soya Oil (Linoleic content 53.3% and saturation of 13.2%) was given to 8 patients in our cardiac clinic as a supplement to a 20 gm. fat diet for 6 to 18 weeks. The dosage used was 27 to 54 gm., three times daily. The resultant blood lipid values showed either no change or a slight rise. Of particular interest was the "after-effect" of the Soya Oil supplementation wherein the elevated lipid levels were maintained for 9 weeks after the oil had been stopped.

In order to investigate this "after-effect" a study was done on a hypercholesterolemic patient over a period of 8 weeks. Baseline studies were obtained on a full diet consisting of 2600 calories, of which 45% were fat, 40% carbohydrate, and 15% protein. This was followed by experimental periods in which 45% of caloric intake was provided by 1) Corn Oil in the form of a formula diet, and 2) isocaloric substitution was made to provide a "fat-free" diet. The patient responded to Corn Oil and to "fat-free" diet. The patient responded to Corn Oil and to "fat-free" feedings by a comparable lowering of serum lipids only when each of the studies was preceded by a full-diet period. When the "fat-free" diet was immediately preceded by a period of high Corn Oil intake, the lipid values, especially the triglycerides, were elevated.

Investigation of this phenomenon is underway at the present time.

The Role of Unesterified Fatty Acids in Lipid Transport and Metabolism.* John J. Spitzer, M.D., and Paul S. Roheim, M.D. (Department of Physiology, Hahnemann Medical College, Philadelphia). Unesterified fatty acids (UFA) play an important role in lipid transport in the blood and serve as

*Supported by the National Heart Institute USPHS.

readily available metabolites for the tissues. The source and disappearance of plasma UFA was studied in normal and in lipemic animals. In the normal dog a difference between femoral vein and artery was found, indicating UFA liberation in the leg due to either lipolysis or mobilization from fat depots. A difference between UFA content of the portal and hepatic veins was also a consistent finding, showing uptake of UFA by the liver. Liberation of UFA in the abdominal region (fat depots?) was indicated by the differences between the portal venous and arterial samples.

The dogs used for the next group of experiments received an intravenous infusion of lymph taken from donor animals that were fed I^{131} labelled triolein. Radioactivity was determined in plasma taken from femoral artery and vein, and from the portal and hepatic vein of the recipient animals. An A–V difference in counts was found during infusion.

To determine whether this difference is due to changes in UFA or esterified fatty acids, UFA, triglycerides, and total and free cholesterol were also estimated. It was found that the V–A differences in UFA that existed in the normal animals disappeared during, and reappeared after, the infusion of lymph. In the same experiments there were no consistent A–V differences in triglycerides in the normal state, but very significant differences appeared during lymph infusion. These differences again disappeared after the infusion. There were no changes in total or free cholesterol contents of the same samples.

Endocrine Aspects of Lipid Metabolism. JOSEPH SEIFTER, M.D., DAVID H. BAEDER, PH.D., AND WILLIAM J. BECKFIELD, M.D. (Wyeth Institute for Medical Research and The Graduate School of Medicine, University of Pennsylvania). It can readily be demonstrated that a variety of steroids, stresses and diseases cause the release of a clearing factor inhibitor (CFI) in the blood. Under conditions not clearly understood at present, CFI can induce hyperlipemia by lipid mobilization (LM). The liver appears to play a critical role in this phenomenon. CFI or LM is released from the posterior pituitary, glucocorticoids being the apparent trigger. The action of LM appears to be limited to mobilization of neutral fat from the mesentery to the liver. There is evidence that LM is not directly involved in the utilization of fat, but that another hormone is necessary. When hyperlipemia occurs as a result of LM action, the liver contributes the excess cholesterol and phospholipid. Persistent elevation of blood lipids by repeated administration of LM does not cause atheromatosis in rabbits. This does not establish that similar lipemias might not produce arterial disease in humans. Lowering the cholesterol induced hyperlipemia by hyaluronidase or hyaluronate does not markedly influence the course of atheromatosis in rabbits. This does not establish that lowering of hyperlipemia is of no benefit to humans. The adrenal-pituitary release of LM represents a common mechanism through which a variety of conditions mobilize fat but is not necessarily the only one, since other endocrines are also involved in lipid storage, mobilization and utilization.

Clinical Studies with a Lipid Mobilizer Hormone. CHRIS J. D. ZARAFONETIS, M.D., JOSEPH SEIFTER, M.D., AND DAVID H. BAEDER, PH.D. (Department of Medicine, Temple University School of Medicine, and Wyeth Institute for Medical Research). The lipid mobilizer hormone (LM) of Seifter and Baeder has been under intensive investigation in these clinical and experimental laboratories. Studies include (1) determi-

nation of the acute response to intravenous injection of LM in fasting patients; (2) metabolic studies in subjects receiving daily injections of LM over a 2-week period; and (3) the effects of prefeeding on the acute response to LM.

Results may be summarized as follows:

1. As little as 1.2 micrograms of crystalline lipid mobilizer hormone (LM) injected intravenously into fasting subjects elicited a prompt two- to threefold rise in plasma fatty acids, cholesterol, and lipid phosphorus. Similar responses were noted with relatively crude plasma dialyzates containing LM when administered in 5 mg. per kilogram amounts.

2. Lipid mobilizer, administered daily for 2 weeks to 4 patients maintained on a diet which provided only 4.8 gm. of fat daily, resulted in a striking elevation of plasma cholesterol, fatty acids, and lipid phosphorus, and a definite increase in urinary and fecal cholesterol excretion.

3. These effects were not observed when LM was administered to 2 other subjects who were maintained on diets providing 99 gm. and 153 gm. of fat daily, respectively.

4. The consequences of prefeeding with glucose, cream, or amino acids on the hyperlipemic effect of LM were studied. Meals of glucose or cream, but not of amino acids, were found to block the hyperlipemic effect of intravenously administered LM.

From these and other studies, it appears that triglyceride mobilization occurs following LM administration, but that prefeeding with glucose apparently enables the liver to metabolize the lipids presented to it, thereby preventing peripheral hyperlipemia. Inhibition of the hyperlipemic effect of LM by prefeeding with cream, however, is probably mediated through a different mechanism than that ascribed to the glucose meals.

These and other observations with LM may hold important implications for certain clinical hyperlipemic states.

BOOK REVIEWS AND NOTICES

INTRODUCTION TO ANESTHESIA. By ROBERT D. DRIPPS, M.D., Professor and Chairman, Department of Anesthesiology, JAMES E. ECKENHOFF, M.D., Professor of Anesthesiology, both of the University of Pennsylvania School of Medicine, both Anesthetist, Hospital of the University of Pennsylvania, AND LEROY D. VANDAM, M.D., Clinical Professor of Anesthesia, Harvard Medical School; Director of Anesthesia, Peter Bent Brigham Hospital. Pp. 266; 27 ills. Philadelphia: W. B. Saunders Company, 1957. Price, $4.75.

THIS comprehensive handbook is peerless for the medical student, intern and anesthesia resident. The overwhelmed novice in anesthesia will find "something to hang his hat on" by reading in a concise and explicit, stepwise manner the order of events from the first patient interview to the actual manipulation of an anesthesia machine, performance of a venipuncture, and the like.

There is consolidated in clear detail the innate perplexities of risk appraisal, patient tolerance, and surgical requirements.

The authors have expertly discussed the two most challenging and ubiquitous questions facing the student and practitioner alike, namely: how deep is the patient and what really constitutes adequate premedication, or conversely, what is the jeopardy of "heavy" medication.

The intriguing role of the reticular system and its relationship to the mechanism of narcosis is presented in an engaging manner.

Timely and worthy of periodic review by all engaged in clinical anesthesia is the discussion of the hazards occurring in the immediate postoperative period.

The bibliography, though not exhaustive, includes many "milestone" monographs.

L. K.

THE ROLE OF HUMORAL AGENTS IN NERVOUS ACTIVITY. By BRUNO MINZ, M.D., Research Professor, National Center of Scientific Research, Department of General Physiology, Sorbonne, Paris, France. Pp. 230; 50 ills. Springfield, Ill.: Charles C Thomas, 1955. Price, $7.75.

THE author recounts the many studies, experiments and hypotheses concerned with this concept in a most objective, unprejudiced and readable manner. He presents the material in a calm, dispassionate language as a true, humble scientist should. This monograph is concerned with neuro-physiology and covers a large amount of material and past history which all clinicians, including internists and psychiatrists as well as neurologists and neuro-surgeons, would do well to have in their libraries and to be familiar with. It has the added advantages of being not too large and there are many references listed at the end of each chapter. There is a good full index at the end. The book is highly recommended to all clinicians. It should be mentioned that the author points out that which is so true, oftentimes a "new" idea or theory or a "new" experiment is in reality not new at all but has been said or done before and perhaps forgotten.

S. G.

ATOMIC RADIATION: THEORY, BIOLOGICAL HAZARDS, SAFETY MEASURES, TREATMENT OF INJURY. Prepared by RCA Service Company, Inc. Reprinted by permission of Wright Air Development Center. Pp. 110; 76 ills. Camden, N.J.: RCA Service Co., Inc., 1957.

THIS pamphlet provides a readable elementary review of nuclear physics and a brief discussion of radiation dosimetery in its first chapter. Next is a short statement of the effects of radiation on various tissues of the body. The third chapter, on shielding and monitoring, contains some simple charts for beta and gamma shielding and illustrations of various monitoring and survey instruments. The specific choice, usefulness, indications and limitations are not discussed. The final chapters, on medical evaluation, and permissible levels, are also elementary.

The manual would seem appropriate as an introduction to the subject for nontechnical persons.

R. R.

DIGITALIS. Symposium, compiled and edited by E. GREY DIMOND, M.D., University of Kansas Medical Center. Pp. 255; 87 ills. Springfield, Ill.: Charles C Thomas, 1957. Price, $7.00.

THE topics of this symposium on digitalis were: Pharmacological basis for therapy (Chen); physiologic actions (Bing); the fate and deposition in animal and man

(Friedman); metabolic fate of radioactive digitoxin (Okita); site of action (Grisolia and Ito); effect on systolic contraction and resting length of ventricular strips (Luisada and Aravanis); new chemicals having a digitalis-like action (Chen); clinical use (Batterman); problems of bedside management (Sodeman); potassium and digitalis (Lown); auricular arrhythmias due to digitalis (Lown). There follows a panel discussion (lively and instructive, as one might expect it). A reprinting of Dr. Major's essay on the life of William Withering and the origins of digitalis in his book starts out the volume. The material presented gives a physiological and pharmacological background including toxicity; and is most useful to the physician in practice, particularly in the clinical portions; certainly, Dr. Batterman's chapter deserves to be read and studied until one knows it by heart.

H. R.

RADIOLOGY SYMPOSIUM, 1954. By Z. M. BACQ, Professor at University of Liege, and PETER ALEXANDER, Royal Cancer Hospital, London. Pp. 362; illustrated. New York Academic Press, Inc., 1955. Price, $9.80.

ATOMIC RADIATION AND LIFE. By PETER ALEXANDER, Royal Cancer Hospital, London. Pp. 239. Baltimore: Penguin Books, 1957. Price, $.85.

FUNDAMENTALS OF RADIOBIOLOGY. By Z. M. BACQ, Professor at University of Liege, and PETER ALEXANDER, Royal Cancer Hospital, London. Pp. 388. New York: Academic Press, Inc., 1955. Price, $6.50.

THESE three books have in common authorship and authority. The audiences for which they will be appropriate differ, the complexity and specialization increasing with the cost.

The Symposium, held at Liege in 1954, brought together many of the world's leading radiobiologists whose papers are collected and presented here. In "Fundamentals," the authors have presented in a somewhat better integrated and unified form, much the same material, representing probably the most current information and views on the subject of radiobiology. The paper bound Penguin edition contains a broadly sketched and admirably proportioned panorama of the same subject material, and is easily the best comprehensive popular account of radiobiology known to the Reviewer. The "Fundamentals" is recommended as the most useful and best proportioned of texts on radiobiology for the serious and technically informed worker. "Atomic Radiation and Life" is enthusiastically recommended as a text for medical students and physicians, and for nonmedical readers of other scientific background. The "Symposium" will be of interest to those who are more advanced workers in the field of radiobiology.

R. R.

ERWORBENE HÄMOLYTISCHE ANÄMIEN: KLINIK UND SEROLOGIE. By PROF. DR. MED. H. H. HENNEMANN. Pp. 198; 26 ills. Leipzig: Georg Thieme Verlag, 1957. Price, DM 26.40.

THIS is an excellent monograph on the acquired hemolytic anemias. The author deals with both the clinical and serologic aspects of this group of disorders. Major sections are devoted to pertinent principles of serology, cold agglutination, hemolysis, incomplete antibodies, and autoantibodies. The references, both European and American, are up-to-date, well-chosen, and well-integrated in the discussions. As might be expected, the illustrations and format are also excellent.

Hematologists and serologists who read German will find much of interest in this volume.

C. Z.

TUMOR SURGERY OF THE HEAD AND NECK. By ROBERT S. POLLACK, M.D., Stanford University School of Medicine. Pp. 101; 49 ills. Philadelphia: Lea & Febiger, 1957. Price, $5.00.

THIS book might best be described as a manual of tumor surgery of the head and neck. The author begins with a discussion on diagnostic procedures and considerations peculiar to tumors in this area. There is a short discussion of the choice between surgery and irradiation therapy and on pre-operative preparation. Concise text and illustrations cover the techniques of resection for each of the various malignancies encountered in the head and neck region. Brevity has been the keynote in this volume, although it should be adequate for the surgeon who has an adequate background in general surgical concepts. It is recommended to those having an interest in tumors in the head and neck areas.

R. B.

ISOTOPIC TRACERS IN BIOLOGY: AN INTRODUCTION TO TRACER METHODOLOGY. By MARTIN D. KAMEN, Associate Professor of Radiochemistry, Washington University Medical School. 3rd ed. Pp. 474; 71 ills. New

York: Academic Press, Inc., 1957. Price, $9.50.

THE presenting of the third edition attests to the excellence, as well as the success, of this book. Its new title indicates one major change, the inclusion of stable as well as radioactive isotopic tracers. The book continues to present, rewritten and modernized, one of the best sections on nuclear physics in any text. It is to be noted for its conciseness as well as completeness. An excellent chapter bridging the gap between reading and actual laboratory procedure is presented. The final section contains a review of applications of tracer methodology in biology and medicine, similar to that in preceding editions.

Although it is not an easy book to read because such a great amount of useful and important information has been compactly presented, this book continues to be recommended for use by all interested in the subject matter. R. R.

LEUKAEMIA AND APLASTIC ANAEMIA IN PATIENTS IRRADIATED FOR ANKYLOSING SPONDYLITIS. BY W. M. COURT-BROWN AND R. DOLL. Pp. 135; illustrated, London: Her Majesty's Stationery Office, 1957. Price, $1.89.

AN increase in the number of deaths from leukemia has been one of the striking features of vital statistics in recent decades. A number of factors undoubtedly have contributed to this increase, with perhaps the most evident being ionizing irradiations. The potential hazards of nuclear radiations led the Medical Research Council to ask the authors to undertake an investigation of patients who had been treated with Roentgen-rays for ankylosing spondylitis. The purpose of the study was to assess the incidence of leukemia and aplastic anemia among them, and to determine if possible the relationship between dosage of irradiation and the subsequent occurrence of these dyscrasias.

The results of this extensive study which embraced some 13,000 patients are given in this report. Their findings should be read not only by hematologists and radiologists, but also by all other physicians who are interested and concerned over the medical problems which have assumed increased significance with the advent of the atomic age.

C. Z.

CLINICAL EXAMINATIONS IN NEUROLOGY. BY SIXTEEN MEMBERS OF THE SECTIONS OF NEUROLOGY AND OF PHYSIOLOGY, MAYO CLINIC AND MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH, GRADUATE SCHOOL, UNIVERSITY OF MINNESOTA. Pp. 370; 76 ills. Philadelphia: W. B. Saunders Co., 1956. Price, $7.50.

"THIS book represents an attempt to convey to two men the gratitude of those who have been apprenticed to them." Thus Alexander R. MacLean begins his dedication of this extraordinary book to the two men who, to have known them was not only to have meant growth in our knowledge, but also of culture and other intangibles which they impressed us with. I say us, because I too, was one of those so apprenticed and so perhaps this review is somewhat prejudiced.

In reading this page after page I am reminded of the fact that the many facts contained were dropped continuously by the men in question. I know of no other place where this material can be obtained so well presented, so simply and clearly and yet so completely. It is a must for all who have any interest in neurology. It is not just a volume on "Examinations in Neurology." There is much more that one has to search in many places to find. The chapter on neuro-ophthalmology is difficult to equal even in a textbook on the diseases of the eye. Emphasis is placed, as it should be and so seldom is, on the value of a careful, painstaking history. Muscle charts, a suggested outline for examining the aphasia patient, and the forms for recording the results of the entire examinations are included. Most excellent chapters on electroencephalography and electromyography could each be separate monographs in themselves. A chapter on mental function emphasizes the fact that neurology and psychiatry should not be so completely divorced as they are in many quarters.

The book is heartily recommended. S. G.

EFFECT OF RADIATION ON HUMAN HEREDITY. Report of a Study Group convened by WHO together with papers presented by various members of the group. Pp. 168; 15 ills. Geneva: World Health Organization, 1957. Price, $4.00.

THIS short manual consists of papers by several members of the Study Group, and a report of the Study Group; many of the world's leading contributors to the subject are represented: Muller, Carter, Wallace, Sievert, Lejeune, Court Brown, Penrose, Neel and others.

The papers and report obviously represent the most highly qualified and current opinion,

and it is a remarkably consistent story the geneticists tell. It would be encouraging to the nongeneticists, of whom the reviewer is one, if there were an opposition party, so that the arguments and conclusions could be subject to challenge and evaluation. In the absence of such opposition, the nongeneticist can only follow the lines of argument and the conclusions, and consider that the conclusions have obtained almost the status of established fact. The Report is essential reading for all interested in this important subject, but is highly technical, and unsuited for popular consumption. R. R.

ANNUAL REVIEW OF MEDICINE. Edited by DAVID A. RYTAND, M.D., AND WILLIAM CREGER, M.D. Pp. 530. Palo Alto, Calif.: Annual Reviews, Inc., 1957. Price, $7.00.

THE problem of keeping apace developments in the many phases of medicine grows progressively more complex. Fortunately, excellent summaries of advances in many important areas appear yearly in this series of Reviews. The present volume maintains the general excellence of its predecessors. Among the topics considered are: Adrenocortical Hormones and the Management of Infections; Infectious Diseases; both Medical and Surgical Aspects of Diseases of the Cardiovascular System; Medical Diseases of the Kidney; Diseases of the Reticulo-Endothelial System and Hematology; Endocrinology; Obstetrics; Diseases of the Nervous System; Psychiatry; Diseases of the Respiratory System; Pediatrics; Special Therapeutics (Helminthic Diseases); and Radioactive Isotopes in Medicine.

This volume is a must for all internists and clinical investigators. C. Z.

THE DIAGNOSIS AND TREATMENT OF PULMONARY TUBERCULOSIS. By PAUL DUFAULT, M.D., Medical Director, Rutland State Sanatorium, Massachusetts. 2nd ed. Pp. 426; 162 ills., and 1 color plate. Philadelphia: Lea & Febiger, 1957. Price, $9.00.

THIS is a second edition of a 1947 text of the same title by Stone and Dufault. It is 100 pages longer and contains almost twice as many illustrations. New chapters have been added: Pathology by A. Reynolds Crane, and Pulmonary Function by Oscar Feinsilver. Drug therapy, and the newer resectional surgical techniques receive appropriate attention. Long stretches are word for word as in the original edition. The illustrations are well chosen but not brilliantly reproduced.

The language is clear, but quite lacking in style or personality. One feels that an effort was made to write in basic English. The reviewer found no serious omissions except failure to advise use of the left lateral decubitus in air embolism. Neglect of this simple procedure can prove fatal.

The book can be recommended to medical students, interns, residents, and physicians in chest hospitals. It does not pretend to be an exhaustive study, but will prove a good guide. Index is included and references are adequate. R. C.

SPONDYLITIS ANKYLOPOETICA (MORBUS STRÜMPELL-MARIE-BECHTEREW). By VICTOR R. OTT, Director of Physical Medicine, University of Giessen, and of Bad Nauheim, and HANS WURM, Director of Pathology, City Hospitals, Wiesbaden. 2nd ed., completely rewritten. Pp. 246; 137 ills. Darmstadt: Verlag Dr. Dietrich Steinkopff, 1957 (International Medical Book Corporation, New York, U.S. Agents). Price, $9.50.

THIS is a detailed presentation of the manifold clinical picture of ankylosing spondylitis, including its modes of onset, natural history and end results. There are discussed the laboratory findings, roentgenographic findings and the problems of differential diagnosis. All aspects of treatment are well described, with due consideration of indications for the several therapeutic modalities and their advantages, disadvantages and undesirable side effects. Of particular merit is the section dealing with the pathology of the disease: a pathology that is in many respects quite characteristic and quite unlike that of any other inflammatory or degenerative joint disease of man. The anatomic review is thorough and complete. The many illustrations and photomicrographs are superb. The book is warmly recommended. H. R.

MODERN THERAPY IN NEUROLOGY. Edited by FRANCIS M. FORSTER, M.D., Dean and Professor of Neurology, Georgetown University School of Medicine. Pp. 792; 4 ills. St. Louis: C. V. Mosby Co., 1957. Price, $12.00.

THIS reviewer finds himself most enthusiastic in his recommendation of this book, not only to the neurologically oriented physician but to all physicians as well. There is, indeed, a surprising amount of material to be found here in a volume which is at the same time not too large and cumbersome. Supplementing the contents are excellent references so

that very easily one may acquaint oneself with where one may read details which are, of course, not possible in a work of this scope. Important, and excellent too, is the very complete index, making use of the book easy.

In addition to the discussion of therapy, which each author has done so well, there is also an adequate consideration of other aspects of the various groups of diseases so that one is not left out in a row-boat without oars 100 miles from shore. The author in each case is an outstanding neurologist whose personal experience, as well as that to be found in the literature, is included in his writing.

This, as so many have said, is a most appropriate book at this time, presenting as it does so many real advances in a field so long considered sterile by so many. It is well worth the price. S. G.

THE GLAUCOMAS. By H. SAUL SUGAR, M.D., Wayne University Medical School. 2nd ed. Pp. 516; 185 ills. New York: Paul B. Hoeber, Inc., 1957. Price, $13.50.

GLAUCOMA is one of the most important problems, and in many ways the most elusive, that the ophthalmologist faces daily. The author covers the whole field in a way that never loses sight of the clinical applications in the forest of research and controversial statistics.

The author does not dare you to disagree with him but gently presents the most accepted views on the subject.

This second edition is brought up-to-date by inclusion of the latest diagnostic techniques. The section on diagnosis is interesting and each type of test is evaluated. The evolution of the pathologic field changes is very lucid.

Antiglaucoma drugs are classified as to their source, indications and site of drug action.

The surgical indications for various types of antiglaucoma operations are given with a detailed description of the technique for doing the more satisfactory procedures.

The reference lists are the tool which enables the author to keep the book within the limits of practical use. At the same time, they enable anyone to trace a particular facet of the disease to the limit desired.

This is an excellent book. It goes a long way toward giving anyone a workable grasp of the subject which can then be used as a base for the inclusive references. L. H.

INTEGRATING THE APPROACHES TO MENTAL DISEASE. Edited by H. D. KRUSE, M.D., Executive Secretary, Committee on Public Health, New York Academy of Medicine, New York City. Pp. 393. New York: Paul B. Hoeber, Inc., 1957. Price, $10.00.

THIS book comprises the transactions of two conferences held under the auspices of the Committee on Public Health of the New York Academy of Medicine. Forty-eight authors explore the subject of the causality of mental disease in an effort to reach a unified concept of psychiatric disorders. The different schools of thought represented could be classified as (1) organic, (2) experimental, psychological, (3) psychodynamic, (4) psychosocial.

Based on similarity in methodology, the organic and the experimental psychological schools showed a mutual understanding, while the psychodynamic and psychosocial disciplines displayed a close relationship.

The latter part of the book deals with an attempt to design a study with an interdisciplinary approach. The difficulties of mutual understanding and of a combined research project is revealed. It is also evident that the psychiatrist has not assumed leadership in collaborative research. This is an essential book to all persons interested in multidisciplinary knowledge and research. M. B.

ENURESIS: A CLINICAL AND GENETIC STUDY. By BERTIL HALLGREN, M.D., Karolinska Institutet, Medical School, Stockholm, Sweden. Pp. 159. Copenhagen: Ejnar Munksgaard, 1957. Price, not given.

THIS monograph details a rather exhaustive clinical and genetic study of 240 children with enuresis and of their siblings and parents in regard to the existence of enuresis and other possibly related factors among them. The data are interpreted as indicating that some instances of enuresis may be genetic in origin. The data will serve in a comparative way for subsequent studies of enuresis. W. N.

THE HANGOVER. By BENJAMIN KARPMAN, M.D., Chief Psychotherapist, St. Elizabeth's Hospital, Washington, D.C. Pp. 531; 16 ills. Springfield, Ill.: Charles C Thomas, 1957. Price, $9.50.

THE hangover, like almost any other human phenomenon, defies definition in its range, sweep, and variability. Except for the mild type, the hangover is an expression of

a neurotic reaction aided and abetted, increased and intensified, by the toxic effects of alcohol.

For the author, the hangover provides a royal road into the emotional life of the alcoholic and affords an intimate understanding of the psychodynamics of alcoholism.

This book is a study of the lives of 7 men and 7 women alcoholics who discuss their family life, their sexual life and their social difficulties. The hangover is symptomatic of the specific underlying personality disorders which lead to alcoholism. M. B.

THE PHYSIOLOGIC BASIS OF GASTROINTESTINAL THERAPY. By HEINRICH NECHELES, M.D., PH.D., Director, Department of Gastro-Intestinal Research, Michael Reese Hospital, and MARTIN M. KIRSHEN, M.D., Professor of Clinical Medicine, Chicago Medical School. Pp. 330. New York and London: Grune & Stratton, Inc., 1957. Price, $8.75.

THE most significant deficiency in recently published texts concerned with the gastrointestinal tract has been the lack of stress on normal and abnormal physiology. The authors, one primarily a physiologist and the other a clinician, have tried to remedy this by providing a text that stresses the fundamental dynamics of disease. The authors have chosen "selected topics" for their consideration but the functions of the gastrointestinal tract as well as their derangements are well covered and most important affections are considered. The etiologic and therapeutic considerations in peptic ulcer are particularly well presented. The only criticism that this reviewer has to make is concerned with those portions of the book devoted to therapy. Both students and clinicians would be even more grateful to the authors, for what is certainly a well conceived and executed text, if they had analyzed more critically the varied therapeutic suggestions quoted from others. S. L.

THE CHRONICALLY ILL. By JOSEPH FOX, PH.D., Executive Director, "The Home for Chronic Sick, Irvington, N.J.. Pp. 229. New York: Philosophical Library, Inc., 1957. Price, $3.95.

THIS thoughtful, concisely written little book presents a sociological approach to the problem of chronic illness. Its author has devoted 20 years in various capacities to the study and analysis of the long-term patient and the aged. The book provides a meaningful account of the problem of rehabilitation today. It tells a story based on the author's experience in the field and includes suggestions and proposals for the solution of some of the problems attending the care and rehabilitation of the chronically ill. The book is not a text on medical treatment; the approach is first to deal with chronic disorders as they strike the individual and only after they have been discussed in that setting, are the problems of organization, institutionalization and the philosophical aspects discussed. The information provided in this book should be of particular interest to the practicing physician, social worker, hospital administrator and to others who are concerned with the problem of chronic illness. M. B.

THE PHYSIOLOGY OF NERVE CELLS. By JOHN CAREW ECCLES, Australian National University, Canberra. Pp. 257; 80 ills. Baltimore: The Johns Hopkins Press, 1957. Price, $5.75.

THIS work is a welcome contribution by an outstanding authority in neurophysiology. It is based on lectures delivered in 1955 at Johns Hopkins with additions and revisions in the light of newer knowledge. Much of the material deals with intracellular potentials and their modification. Synaptic responses of individual cells are emphasized. Both excitatory and inhibitory reactions of nerve cells are included. Synaptic transmitter substances are well presented. This book is an essential one for students and researchers in neurophysiology. In most cases the illustrations are well chosen and lucid. M. O.

THE TEACHING OF HYGIENE AND PUBLIC HEALTH IN EUROPE: A REVIEW OF TRENDS IN UNDERGRADUATE AND POSTGRADUATE EDUCATION IN NINETEEN COUNTRIES. By F. GRUNDY, M.D., Professor of Preventive Medicine, Welsh National School of Medicine, Cardiff, and J. M. MACKINTOSH, M.D., Professor of Public Health, University of London. Pp. 254, Geneva: World Health Organization, 1957. (Distributed in the U.S.A. by Columbia University Press.) Price, $5.00.

THIS volume, number 34 in the World Health Organization Monograph Series, provides a comprehensive review of current European teaching designed for the promotion of health and the prevention of disease. The role and position of hygiene and public health in the medical curriculum, with pertinent

teaching methods and procedures, are thoroughly examined.

An historical analysis of changing concepts in public health comprises the first 2 chapters. Undergraduate education in hygiene, preventive and social medicine is described in the following 7 chapters; 5 subsequent chapters are directed to postgraduate education in public health. The last section, Chapter 15, summarizes observations on curricula in 19 individual countries, from Austria to Yugoslavia. Recent European study conferences on related undergraduate and postgraduate training, held in France (1952) and Sweden (1953) under the auspices of WHO, are appended as annexes to this indexed volume.

This book is recommended for all interested in the disciplines of preventive medicine and community health and their relationships with other branches of medical practice, teaching and research. F. R.

Medicine and Writing. By Russell L. Cecil, Morris Fishbein, John F. Fulton, Joseph Garland, Douglas Guthrie and Felix Martí-Ibanez. Pp. 65; 6 ills. New York: MD Publications, Inc., 1957. Price, not given.

This symposium includes six articles on writing in some medical fields in which their authors have proved their expertness: Cecil, The Editing of a Modern Medical Text Book; Fishbein, Plain Talking and Clear Writing; Guthrie, On Writing a History of Medicine; Garland, The Art of Communication; Fulton, The Principles of Bibliographic Citation; Marti-Ibañez, Minerva and Aesculapius: The Physician as Writer. Any physician who writes will here find much that is interesting as well as helpful. R. K.

An Atlas of Cardiac Surgery. Prepared by Jorge A. Rodriguez, M.D., Assistant Professor of Surgical Anatomy and Research Associate. Department of Surgery, University of Mississippi Medical School. Pp. 250; 125 ills. Philadelphia and London: W. B. Saunders Company, 1957. Price, $18.00.

This "Atlas of Cardiac Surgery" consists of an appropriate text with line drawings to illustrate the subject matter. The unique feature about this Atlas is that it represents the work and method of many prominent surgeons interested in the field. The book covers its subject very completely, very concisely and with excellent illustrations.

Although this Atlas is in a rapidly advancing field there is much basic information recorded here that will not change, such as the anatomical relationships given. Therefore, the book provides a very excellent point of reference for those interested in this phase of surgical activity. R. T.

Medical Physiology. Edited by Philip Bard, Professor of Physiology, School of Medicine, The Johns Hopkins University, 10th ed. Pp. 1276; 438 ills., 5 in color. St. Louis: C. V. Mosby Co., 1957. Price, $14.00.

Although based on MacLeod's text of 16 years ago this present work is very new. It is fitted for medical students, medical scientists and practitioners of medicine. The most important material needed to support a given statement has been chosen in almost every case. Although many of the figures are those of the previous editions they are obvious choices to illustrate the points intended. As one would expect the chapter on Respiration by Dr. Carl F. Schmidt is superb. It presents the current situation and modern concepts in a way which will be appreciated by all those concerned with this field. The book is well organized and despite the fact that some of the best small sections are relegated to fine print, it can be recommended without hesitation. M. O.

Degenerative Changes in the Sternoclavicular and Acromioclavicular Joints in Various Decades. By Anthony F. DePalma, M.D., Professor of Orthopaedic Surgery, Jefferson Medical College. Pp. 178; 105 ills. Springfield, Ill.: Charles C Thomas, 1957. Price, $5.50.

This text primarily reports the gross and microscopic findings of the sternoclavicular and acromioclavicular joints in successive decades from the first decade through the tenth decade. This includes variational anatomy and degenerative changes. In all, 223 sets of these joints were studied. The clavicle and its gross morphology were thoroughly studied as well.

Roentgenographic investigation was also a part of the study. This area includes only three illustrations and, by contrast, this part of the investigation appears superficial to this reviewer.

The subject matter reviewed certainly indicates much time and work were necessary for its completion. The text is adequately

illustrated. In general, it should be welcomed by the students of anatomy. Its extensive use by the clinician is doubtful. A. S.

NEW BOOKS

A Word to Parents about Mental Hygiene. By Leo Kanner, M.D., Director, Children's Psychiatric Service, The Johns Hopkins Hospital. Pp. 86. Madison, Wisconsin: The University of Wisconsin Press, 1957. Price, $1.00 Paper; $3.00, Cloth.

Kanner has wrapped his working hypothesis of personality development of children into a neat and useful package. This book can be exceedingly helpful for thoughtful parents and especially for those who find themselves a bit confused with current theories of child rearing. It can also be read with profit by others such as teachers, social workers and physicians who have opportunities to "guide" children and their parents. W. N.

Le Champ Electrique du Coeur Normal et Pathologique. Etude Expérimentale. By P. B. Avril, Cardiac Department of Medical School of Marseille, France. Pp. 183; 73 ills. and 2 color plates. Paris: Masson et Cie, 1956. Price, 1.800 fr.

This important experimental study on the dog's heart analyzes the electrical field inside and on the surface of the chest. Three planes parallel to the equatorial zone of the ventricles are studied, using a ten channel electroencephalograph. Normal findings as well as those obtained by producing right bundle branch block and focal lesions are presented. It is shown that the electric field is but little modified when placing a rubber bag around the heart. A special study is made as to the significance of the subepicardial layers for the formation of the electrocardiogram. There are excellent illustrations and 354 references. The book is highly recommended to those interested in cardiac electrophysiology. H. R.

An Introduction to Electromyography. By Fritz Buchthal, M.D., Professor of Neurophysiology, University of Copenhagen. Pp. 43; 8 ills. Copenhagen: Glydendals Presseafdeling, 1957. Price not given.

The Ordeal of Gilbert Pinfold. By Evelyn Waugh. Pp. 232. Boston and Toronto: Little, Brown & Company, 1957. Price, $3.75.

Mr. Waugh suffered a brief bout of hallucination and the story he tells is based on this personal experience. He believes others who have had similar experiences, will find the tale amusing. This reviewer regards this book as another instance of the author's skill as a novelist. M. B.

Physiology of Prematurity. Transactions of the First Conference, March 21, 22, and 23, 1956, Princeton, N.J. Edited by Jonathan T. Lanman, M.D., Department of Pediatrics, New York University-Bellevue Medical Center. Pp. 151; 42 ills. New York: The Josiah Macy, Jr. Foundation, 1957. Price, $3.25.

This volume contains the edited transactions of the First Conference on Physiology of Prematurity supported by The Josiah Macy, Jr. Foundation. The topics of the conference were Fetal-Maternal Endocrinology in Late Pregnancy introduced by Jonathan T. Lanman and The Fetal and Placental Circulation in Late Pregnancy introduced by Geoffrey S. Dawes. The editing of the group discussion on each topic is well done. This volume will be of interest to investigators in these fields. W. N.

Science Looks at Smoking. By Eric Northrup. Pp. 190. New York: Coward-McCann, Inc., 1957. Price, $3.00.

A medical journalist's survey of the numerous conflicting reports on smoking as a possible cause of lung cancer and coronary artery disease, with an introduction by Dr. Harry S. N. Greene, Chairman of the Department of Pathology of Yale University. This volume, intended chiefly for the laity, attempts to evaluate both statistical studies, such as that of Hammond and Horn, and reports of experimental efforts to produce cancer in laboratory animals by use of tobacco products. Much emphasis is placed on the limitations of these methods, which the author feels "have failed to establish a valid scientific case" for the etiological relationship to lung cancer. The Auerbach report, citing a high frequency of pre-cancerous lesions in the bronchial mucosa of heavy smokers examined at necropsy, is discounted as "interesting, but as yet inconclusive." In the author's opinion, air-pollution in urban areas is a hazard of greater magnitude than smoking. C. N.

New Research Techniques of Neuroanatomy. Edited by William F. Windle, Ph.D., Sc.D., National Institute of Neurological Diseases and Blindness, National Institutes of Health. Pp. 98; 25 ills. Springfield, Ill.: Charles C Thomas, 1957. Price, $4.75.

The new vistas opened to the neuroanatomists by recent technical developments are exposed in this symposium. Electromicroscopy has become an important tool in revealing structural details of the neuron as shown by Palay. New silver impregnations have been developed by Nauta for demonstration of degenerating axons and by Rasmussen for the study of synaptic endings. Murray reports how tissue culture may be of value to the morphologist as well as the biochemist and pharmacologist, for example, for

study of electrical phenomena or of the action of various substances such as serotonin. Local blood flow in neural tissue can be measured by radioautography using an inert radioactive gas, trifluoroiodomethane as shown by Soloff. Histochemical localization of acetylcholinesterase is outlined by Koelle, and Albers presents enzyme studies. In his concluding remarks Dempsey aptly points to the dangers inherent in too rapid progress and the necessity of validating the new methods, for example, electromicrographs, with the results obtained by the classical methods.

E. S.

Epilepsy: Grand Mal, Petit Mal, Convulsions. By Letitia Fairfield, C.B.E., M.D., D.P.H. Pp. 159; 8 ills. New York: Philosophical Library, Inc., 1957. Price, $4.75.

This is a discussion by a physician for the lay public of a serious, common problem. It covers the subject quite adequately and well in understandable language. It should be read by all who have any interest in those who suffer from the disease, from anxious parents to employers, to nurses and so on. The discussion is from the English point of view and this, in some aspects, is a bit different from the American.

It is recommended even though the author suggests that the patient "most probably" will not have to take drugs all his life and so is more optimistic as to cure than is the reviewer.

S. G.

Chronicle of the World Health Organization, Vol. 11, No. 6–7, June–July, 1957. Pp. 60; 6 ills. Geneva: World Health Organization, 1957. Price, $.70.

Proteolytic Enzymes and Their Clinical Application. By Gustav J. Martin and 37 others. Ann. New York Acad. Sci., **68**, 1, 1957. Pp. 244; 60 ills. New York: New York Academy of Sciences, 1957. Price, $3.50.

Biological Applications of Infrared Spectroscopy. By Robert P. Bauman, Carl Clark and 30 others. Ann. New York Acad. Sci., **69**, 1, 1957. Pp. 254; 107 ills. New York: New York Academy of Sciences, 1957. Price, $3.50.

Determination of Sr^{90} and Ba^{140} in Bone, Dairy Products, Vegetation, and Soil. By H. L. Volchok, J. L. Kulp, W. R. Eckelmann, and J. E. Gaetjen. Ann. New York Acad. Sci., **71**, 293, 304. Pp. 11. New York: New York Academy of Sciences, 1957. Price, $.75.

Modern Ideas on Spontaneous Generation. By Ross F. Nigrelli and 18 others. Ann. New York Acad. Sci., **69**, 255, 1957. Pp. 121; 28 ills. New York: New York Academy of Sciences, 1957. Price, $2.50.

The Role of I^{131}-Labeled Proteins in Biology and Medicine. By S. P. Masouredis and 21 others. Ann. New York Acad. Sci., **70**, 1, 1957. Pp. 152; 53 ills. New York: New York Academy of Sciences, 1957. Price, $3.00.

Expert Committee on Insecticides. Seventh Report. WHO Technical Report Series No. 125. Pp. 31, 1 ill. Geneva: World Health Organization, 1957. Price, $.30.

General Principles Governing the Use of Food Additives. First Report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series No. 129. Pp. 22. Geneva: World Health Organization, 1957. Price, $.30.

NEW EDITIONS

Textbook of Physiology and Biochemistry. By George H. Bell, B.Sc., M.D. (Glasg.), University of St. Andrews at Queen's College, Dundee; J. Norman Davidson, M.D., D.Sc. (Edin.), University of Glasgow; and Harold Scarborough, M.B., Ph.B. (Edin.), Welsh National School of Medicine of the University of Wales. 3rd ed. Pp. 1068; illustrated. Baltimore: The Williams & Wilkins Co., 1956. Price, $12.00.

This current edition of a valuable text is extensively revised. It presents a unique combination of the two fields indicated in the title. The material is very well presented. The choice of diagrams and pictures is excellent. It can safely be recommended for medical students as a means of reviewing the correlation between Chemistry and Physiology. The references recommended are in general basic to the area represented. M. O.

Manual of Nutrition. By Magnus Pyke, Ph.D., F.R.I.C. 4th ed. Pp. 70; 2 ills. New York: Philosophical Library, Inc., 1957. Price, $3.50.

This manual was prepared for the purpose of acquainting the general public and, particularly, the teachers and students of home economics with the principles of the science of nutrition. The definitions and brief discussions of nutrients, digestive processes and utilization of food factors are presented in a simple fashion. The nutrional

education of the lay public, for whom it is intended, would be advanced by the reading of this book. C. S.

Surgical Technique and Principles of Operative Surgery. By A. V. Partipilo, M.D., Clinical Professor of Surgery, The Stritch School of Medicine of Loyola University. 6th ed. Pp. 966; 1235 ills., 4 in color. Philadelphia: Lea & Febiger, 1957. Price, $20.00.

This is an excellent text for the surgical resident. While Dr. Partipilo is the major contributor, there are 18 other contributors. The text very adequately covers operative surgery and technique, beginning with fluid therapy, blood transfusion and anesthesia, as well as the use of radioisotopes, down through a system of surgery that involves the entire field of General Surgery. Of particular interest are his excellent illustrations of knot typing and the anatomical considerations upon which are based the techniques of surgery. This book is up-to-date and is recommended reading, particularly for the resident surgeon.

R. T.

The Chemistry of Organic Medicinal Products. By Glenn L. Jenkins, Purdue University, Walter H. Hartung, Medical College of Virginia, Kenneth E. Hamlin, Jr., Abbott Laboratories, and John B. Data, Purdue University. 4th ed. Pp. 569; 2 ills. New York: John Wiley & Sons, Inc., 1957. Price, $10.75.

This is a completely revised edition of a well-known textbook and reference volume. Except for antibiotics, which are grouped together, the medicinal agents are arranged according to chemical classification rather than according to pharmacologic actions or therapeutic uses. Only relatively brief treatment is given each agent; however this concise volume is well documented by references to more extensive literature up to April, 1956. Structure-activity relationships are not dealt with extensively, although some groups of compounds are rather well covered in this respect. The book includes one chapter on stereoisomerism and a final chapter on physicochemical properties of medicinal products. The book is well indexed. This should prove to be a useful book, particularly for pharmacists, pharmaceutical chemists, and pharmacologists.

R. S.

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